BIOCHEMISTRY OF HORMONES

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Final Section
Pancreatic hormones

The pancreas is a mixed exocrine and endocrine gland that plays a central role in digestion and in the metabolism, utilization, and storage of energy substrates. Normal pancreatic function involving the production and release of the hormones insulin and glucagon is essential for the physiologic control of glucose homeostasis.
Physiological anatomy of the pancreas

Consist of two major tissues
1. The Acini which secrete digestive juices into the duodenum
2. Islets of Langerhans which consists of three major types of cells distinguished from each other by their structure and staining characteristics.

**Alpha** cells secrete Glucagon

**Beta** cells secrete insulin

**Delta** cells secrete Somatostatin.

**F (PP)** cells secrete Pancreatic polypeptide, that stimulates gastric chief cells, inhibits bile and pancreatic secretion, and intestinal motility.
Pancreatic Hormones (Insulin)

Insulin is synthesized as pre-proinsulin (removal of signal peptide in ER)

Proinsulin (86 a.a) →

Insulin (51 a.a) + Connecting C-peptide (35 a.a)
GLUCOKINASE
(also known as hexokinase IV)
the “glucose sensor”?

Increase concentration of glucose in the Blood, after a meal, leads to increased ATP production in the pancreatic b-cell and this in turn reduces K+ outflow, leading to membrane depolarisation. The subsequent Ca2+ entry constitutes the secretion signal.
Regulation of insulin secretion

Direct stimulation
Increased plasma glucose or a.a. levels directly stimulate \( \beta \) cells

Hormonal regulation
Gastrointestinal hormones (GIP, CCK) directly stimulate \( \beta \) cells

Neural regulation
Parasympathetic nervous system stimulates \( \beta \) cells
Sympathetic NS inhibits \( \beta \) cells

Other Stimuli that \( \uparrow \) cAMP also \( \uparrow \) insulin. K+ depletion (hyperaldosteronism, diuretics)
\( \rightarrow \) insulin \( \downarrow \downarrow \)

Diet
High carbohydrate diet \( \rightarrow \) \( \beta \) cell hypertrophy \( \rightarrow \) increased insulin secretion followed by \( \beta \) cell exhaustion?? or receptor down regulation

Drugs
Sulfonylurea derivatives - close ATP-sensitive K+ channels \( \rightarrow \) insulin \( \uparrow \uparrow \)
Insulin Metabolism

- Rapidly metabolized in liver (80%) Kidney and placenta.
- Half-life of about 5 minutes
- Degraded by hepatic glutathione insulin dehydrogenase
- Enzyme disrupts S-S bonds
Physiological effect of Insulin

Insulin receptors are widespread, more specific effect (85%) on skeletal muscles

- Glucose transport into cells particularly muscle and adipose tissues.
- Glycolysis
- Glycogenesis
- Lipogenesis (adipose tissue)
- Lipolysis (inhibited)
- Amino acid transport in to cells (specially muscle and liver)
- Protein synthesis

- Overall promotes energy storage (anabolism)
- Depressed energy formation (catabolism)
- Released during meal (fed state)
- Basal level necessary
INSULIN

LIVER

glycogenesis
Glycolysis

(glut2)
(insulin-independent)

ADIPOSE TISSUE

αGlycerol phosphate

NEFA

lipogenesis

Glucose

MUSCLE

Glycogenesis
Gluconeogenesis
GROWTH AND DEVELOPMENT

INSULIN

Stimulate

SOMATOSTATIN

Decreases

GLUCAGON

 Increases

BLOOD GLUCOSE

negative
Insulin receptors

The insulin receptor is a heterotetrameric glycoprotein membrane receptor composed of 2 α and 2 β-subunits, linked by disulfide bonds. The α -chain is the extracellular portion and is the site for insulin binding. The β -chain consists of a short extracellular region, a transmembrane segment, and an intracellular segment that has intrinsic tyrosine kinase activity controlled by insulin binding to the extracellular α -subunit.
Signal transduction pathway for insulin

Insulin binding to the receptor triggers receptor autophosphorylation on tyrosine residues in the cytoplasmic domain (α-chain). The activated receptor phosphorylates several insulin receptor substrates (IRS-1, -2, -3, -4) on multiple tyrosine residues. These IRS proteins facilitate the interaction of the insulin receptor with intracellular substrates by serving as a scaffold for recruitment of proteins involved in signal transduction to downstream pathways. The result is coupling of insulin receptor activation to signaling pathways, mainly the phosphatidylinositol-3-kinase (PI3 kinase) and the mitogen-activated protein kinase (MAPK) pathways.
IR signaling pathways.

Le Roith D, Zick Y Dia Care 2001;24:588-597
HORMONAL REGULATION OF BLOOD GLUCOSE

- Insulin
- Increase
- Decrease

Adrenaline, Glucagon, Cortisol, Somatotrophin
Glucagon

Initially synthesised as proglucagon precursor (160aa)

• Single chain polypeptide (29aa)
• Binds to G protein –coupled receptor
• Mechanism of action: activation of adenyl cyclase/cAMP second messenger system
• short half-life (5–10 minutes) degraded mostly in the liver.
• The prohormone proglucagon is expressed not only in the pancreas, but also in other tissues, such as enteroendocrine cells in the intestinal tract and in the brain.
Regulation of glucagon release

Decreased Blood glucose

- Certain amino acids
- Some GI hormones
- Sympathetic actions
- Para sympathetic actions
- Somatostatin

α-Cells

- +ive
- -ive

β-Cells

Glucagon

δ-cells

Raised Blood Glucose
Physiological effect of Glucagon

Released in **fasting** state
Potent stimulator of hepatic glycogenolysis
Stimulates hepatic uptake of glucogenic amino acids
Stimulates hepatic gluconeogenesis
Stimulates hepatic ketogenesis (production of ketone bodies from fatty acid precursors)
Somatostatin

- 14–amino acid peptide hormone produced by the -cells of the pancreas.
- Its release is stimulated by high-fat, high-carbohydrate, and particularly protein-rich meals, and is inhibited by insulin.
- Has a generalized inhibitory effect on virtually all gastrointestinal and pancreatic exocrine and endocrine functions.
- Exogenous administration of somatostatin suppresses the release of both insulin and glucagon.
Pancreatic Polypeptides

Pancreatic polypeptide is a 36–amino acid peptide hormone that belongs to a peptide family including neuropeptide Y and peptide YY. It is produced in the endocrine type F cells located in the periphery of pancreatic islets and is released into the circulation after ingestion of food, exercise, and vagal stimulation. The effects of pancreatic polypeptide include inhibition of pancreatic exocrine secretion, gallbladder contraction, stimulation of glucocorticoid secretion, modulation of gastric acid secretion, and gastrointestinal motility. Pancreatic polypeptide crosses the blood-brain barrier and has been postulated to play a role in regulating feeding behavior.
Glucose homeostasis

Addition of glucose blood from food digestion

Hyperglycemia

Liver - hydrolyzes glycogen and releases glucose into the blood

Liver - removes glucose from the blood and produces glycogen from it

Glucagon

Pancreatic Beta Cells

Pancreatic Alpha Cells

Stimulate

Inhibit

Insulin

Pancreas

Hypoglycemia
Diabetes mellitus
Defined as a group of diseases characterized by high levels of blood glucose resulting from defects in insulin production, insulin action, or both.

Type 1 Diabetes when $\beta$-cells are destroyed, also called insulin depended diabetes. Onset is usually in younger peoples. Before age30.

• Type 2 Diabetes also called insulin independent as the cells become resistant to insulin eventually leads to $\beta$-cells failure. More common in obese people. Very common in Saudi Arabia.

Gestational Diabetes:
When blood glucose rises in pregnancy. Prevalence in Saudi Arabia is nearly 9%.
Main symptoms of Diabetes

Central
- Polydipsia
- Polyphagia
- Lethargy
- Stupor

Eyes
- Blurred vision

Systemic
- Weight loss

Respiratory
- Kussmaul breathing (hyper-ventilation)

Breath
- Smell of acetone

Gastric
- Nausea
- Vomiting
- Abdominal pain

Urinary
- Polyuria
- Glycosuria

blue = more common in Type 1
Symptoms of diabetes

- Excessive thirst; frequent urination (polyuria); large intake of water (polydipsia). These changes are due to excretion of large amounts of glucose in the urine (glucosuria) that cause osmotic diuresis.

- Excessive but incomplete oxidation of fatty acids in the liver, resulting in overproduction of the ketone bodies acetoacetate and \(-\)hydroxybutyrate. Acetoacetate can convert to acetone, found in the blood of diabetics (breath odor like acetone).

- The overproduction of ketone bodies is called ketosis, and their production is accompanied by decreased blood pH, (acidosis) or ketoacidosis, which can eventually leads to diabetic coma.
Diagnosis

Fasting Plasma Glucose Test (FPG) - (cheap, fast)
  * fasting B.G.L. 100-125 mg/dl signals pre-diabetes
  * >126 mg/dl signals diabetes.

Oral Glucose Tolerance Test (OGTT)
  * tested for 2 hrs after glucose-rich drink
  * 140-199 mg/dl signals pre-diabetes
  * >200 mg/dl signals diabetes
In Diabetes

Hyperglycemia

- Normal renal glucose excretion
- Transport system for glucose (coupled to Na+) in proximal convoluted tubule
- Threshold blood [glucose] corresponding to renal transport maximum ~10mM

Blood glucose ≥15mM

Glucose now present in the urine

Osmotic diuresis

Blood glucose (~ 5mM)

Normally all reabsorbed in proximal tubule

Glucose free urine
Treatment

Type I Diabetes
• Insulin replacement, (recombinant human insulin)

Type 2
• Diet
• Exercise
• Drugs to stimulate insulin release and its action.
• Vitamin D
• Final stage: insulin
Adrenal Gland

The adrenal glands are located above the kidneys. They are small, averaging 3–5 cm in length, and weigh 1.5–2.5 g. They are made of 2 different components derived from 2 distinct embryologic origins: the cortex and the medulla.

The outer adrenal cortex is derived from mesodermal tissue and accounts for about 90% of the weight of the adrenals.
Functional Anatomy of adrenal cortex
Three distinct zones

- Mineralocorticoids (Aldosterone)
- Glucocorticoids (Cortisone)
- Androgens
- Epinephrine and norepinephrine
All adrenal cortex hormones are steroids, they are not stored, synthesized as needed.
• The first step is the conversion of cholesterol to pregnenolone with the help of the enzyme cytochrome P450 side-chain cleavage enzyme (P450scc) present in the inner mitochondrial membrane.
• Different zones of the adrenal cortex have different relative activities of enzymes present in ER, which results in different chemical reactions taking place.
Pregnenolone can be converted into three different pathways, depending upon whether to make mineralcorticoids, glucocorticoids, or androgens:
Hormones of the Adrenal Cortex

Figure 9.10
Stress

Circadian rhythm

Hypothalamus

↑ CRH secretion

Anterior pituitary

↑ ACTH secretion

Adrenal cortex

↑ Cortisol secretion

Negative feedback
Mineral Corticoid action

• Aldosterone exerts the 90% of the mineralocorticoid activity. Cortisol also have mineralocorticoid activity, but only 1/400\textsuperscript{th} that of aldosterone

• Aldosterone increases renal tubular (principal cells) reabsorption of sodium & secretion of potassium

• Excess aldosterone ↑ ECF volume & arterial pressure, but has only a small effect on plasma sodium concentration
Aldosterone

• Excess aldosterone causes hypokalemia & muscle weakness, & too little aldosterone causes hyperkalemia & cardiac toxicity

• Excess aldosterone increases tubular (intercalated cells) hydrogen ion secretion, with resultant mild alkalosis

• Aldosterone stimulates sodium & potassium transport in sweat glands, salivary glands, & intestinal epithelial cells
Aldosterone

Plasma membrane

Ribosome

mRNA

DNA

Aldosterone–receptor complex

mRNA synthesis

Proteins produce a response.
Action of Glucocorticoid

Effect of cortisol on protein metabolism

• Reduction of protein storage in all cells except those of liver – ↑ protein catabolism & ↓ protein synthesis

• Cortisol increases liver & plasma proteins

• Mobilizes aminoacids from non hepatic cells, thus increase blood amino acid level.

• ↑ amino acid transport to liver cells & ↓ transport of amino acids into other cells
REGULATION OF CORTISOL SECRETION

**HYPOTHALAMUS**

- CRH

**ANTERIOR PITUITARY**

- ACTH

**ADRENAL CORTEX**

- CORTISOL

**TARGET ORGANS**

- INCREASED BLOOD GLUCOSE
- INCREASED BLOOD AA
- INCREASED BLOOD FATTY ACIDS

**STRESS**

- DIURNAL RHYTHM
Aldosterone as part of the renin-angiotensin-aldosterone system

In contrast to glucocorticoids, which are under exclusive neuroendocrine regulation, aldosterone synthesis and release in the adrenal zona glomerulosa are predominantly regulated by angiotensin II and extracellular $K^+$ and, to a lesser extent, by ACTH.
Regulation of Na+ ion concentration

- Low Na+ intake
  - Low plasma Na+ concentration
    - Hypothalamus
      - Posterior pituitary
        - ADH
          - Water reabsorption in collecting ducts
            - Urine volume
              - Sympathetic nerve activity
            - Blood volume
              - Juxtaglomerular apparatus
  - Na+ retention in blood
    - Na+ reabsorption in cortical collecting duct
      - Aldosterone
        - Adrenal cortex
          - Angiotensin II
            - Renin
Control of blood pressure by aldosterone

Angiotensin II can raise blood pressure by:
- vasoconstrictor effects.
- stimulating aldosterone secretion
Disorders of Adrenal cortex

1. Hypoaldosteronism
   loss of water/Na+
   Addison’s disease – low aldosterone & cortisol

2. Hyperaldosteronism
   Cushing’s syndrome (hypersecretion of cortisol, androgens, aldosterone)
Androgens

DHEA is the most abundant circulating hormone in the body and is readily conjugated to its sulfate ester DHEAS. Its production is controlled by ACTH. Although much of the physiology of DHEA and DHEAS is still not completely understood, in females they may contribute to libido. About half of the body's DHEA is produced in the adrenal cortex — with the rest coming from gonads, fat tissue and (notably) the brain. The steroid synthesis pathway is:

\[
\text{cholesterol} \rightarrow \text{pregnenolone} \rightarrow \text{DHEA} \rightarrow \text{testosterone} \rightarrow \text{estrogen}
\]
Blood levels are highest in the developing foetus, drop sharply after birth, begin climbing again at age 6–8 (a time of rapid growth) to a peak at age 25–30 and then decline to about 10% of the peak level by age 80. The clinical impact of this age-related deficiency in DHEA production is not fully understood but may play an important role in the regulation of immune function and intermediary metabolism, among other aspects of human physiology.
Adrenal Medulla

- Produces two similar hormones (catecholamines)
  - Epinephrine
  - Norepinephrine

- These hormones prepare the body to deal with short-term stress
Catecholamine Synthesis

tyrosine

\[ \text{tyrosine hydroxylase} \]

dihydroxyphenylalanine

\[ \text{L-aromatic amino acid decarboxylase} \]

dopamine

\[ \text{dopamine-β-hydroxylase} \]

norepinephrine

\[ \text{phenylethanolamine-N-methyltransferase} \]

epinephrine
Release Of Catecholamine
Release Of catecholamine

The release of catecholamines is a direct response to sympathetic nerve stimulation of the adrenal medulla. Acetylcholine released from the preganglionic sympathetic nerve terminals binds to nicotinic cholinergic receptors in the plasma membrane of the chromaffin cells, depolarizing the cells. Depolarization of the cells leads to activation of voltage-gated Ca\(^{2+}\) channels, producing an influx of Ca\(^{2+}\). The synaptic vesicles containing the preformed catecholamines are docked beneath the synaptic membrane and are closely associated with voltage-gated Ca\(^{2+}\) channels. The influx of Ca\(^{2+}\) triggers the exocytosis of secretory granules, which release their contents (catecholamines, chromogranins, ATP, adrenomedullin, proopiomelanocortin products, and other peptides) into the interstitial space, from where they are transported in the circulation to their target organs.
Norepinephrine release and Recycling

1. Action potential arrives at the varicosity.
2. Depolarization opens voltage-gated Ca^{2+} channels.
3. Ca^{2+} entry triggers exocytosis of synaptic vesicles.
4. NE binds to adrenergic receptor on target.
5. Activity ceases when NE diffuses away from the synapse.
6. NE is transported back into the axon.
7. NE can be taken back into synaptic vesicles for re-release.
8. NE is metabolized by monoamine oxidase (MAO).

KEY
- NE (norepinephrine)
Catecholamine Transport and Metabolism

The half-life of circulating catecholamines is short and is estimated to range from 10 seconds to 1.7 minutes. A fraction of the catecholamines released circulate bound to albumin with low affinity. Catecholamine metabolism occurs mainly in the cytoplasm of the same cells where they are synthesized following leakage from cytoplasmic vesicles.

Monoamine oxidase (MAO) and Catechol-o-methyl transferase (COMT) are the main enzymes involved in catabolism of catecholamine.
Metabolism of catecholamine

The joint action of MAO and COMT on norepinephrine and epinephrine produces the metabolite vanillylmandelic acid, which is then excreted in the urine;
Mechanism of Action of Catecholamine

The systemic effects of catecholamines are mediated by binding to cell membrane G protein–coupled receptors distributed widely throughout the body. These G protein–coupled receptors have differential effects depending on the subtype of G protein to which they are associated and the signal transduction mechanism linked to that specific G protein. The adrenergic receptors are classified as

- stimulatory receptors (α) or
- predominantly inhibitory receptors (β)).
<table>
<thead>
<tr>
<th>Receptor</th>
<th>Effectively Binds</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\alpha-1)</td>
<td>Epinephrine &amp; norepinephrine</td>
<td>(\uparrow) Ca+ ions, myocardial contractility, Hepatic Glu-metabolism</td>
</tr>
<tr>
<td>(\alpha-2)</td>
<td>Epinephrine &amp; norepinephrine</td>
<td>(\downarrow) cAMP, blood pressure homeostasis</td>
</tr>
<tr>
<td>(\beta-1)</td>
<td>Epinephrine &amp; norepinephrine</td>
<td>(\uparrow) cAMP regulates contraction and relaxation of cardiac myocytes</td>
</tr>
<tr>
<td>(\beta-2)</td>
<td>Epinephrine</td>
<td>(\uparrow) cAMP vasodilatation, bronchial smooth muscle relaxation, lipolysis</td>
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2/10/2013
Adrenergic Receptors

For many of these receptors, their precise physiologic functions and their therapeutic potential have not been fully elucidated. Only for the $\beta_1$-adrenergic receptors have subtype-selective ligands been developed that have helped to identify the physiologic significance of $\beta_1$, $\beta_2$, and $\beta_3$ receptors, some of which are now used in clinical medicine.

Selective agonists such as **isoproterenol** for the $\beta_2$-adrenergic receptor play an important role in asthma therapy, $\beta_1$-receptor antagonists are first-line medication for patients with hypertension, coronary heart disease, or chronic heart failure.
Regulation of androgenic receptors

- Chronic exposure to receptor agonists, the number of receptors in the plasma membrane can be reduced because of decreased synthesis of the receptor (down-regulation).
- Glucocorticoids and thyroid hormone up-regulate the androgenic receptors by increased transcription of the gene for the receptor.
Physiological effect of Catecholamine

Alarm Phase

"Fight or Flight"
Immediate short-term responses to crises

Brain

Sympathetic stimulation

General sympathetic activation

Epinephrine
Norepinephrine

Adrenal medulla

1. Mobilization of glucose reserves
2. Changes in circulation
3. Increases in heart and respiratory rates
4. Increased energy use by all cells
Catecholamine activity

Stimulates the “fight or fight” reaction
Increased plasma glucose levels
Increased cardiovascular function
Increased metabolic function
Decreased gastrointestinal and genitourinary function
Action of epinephrine

[Diagram showing the action of epinephrine on muscle, liver, and adipose tissue]

2/16/2013
Diseases of Overproduction & Undersecretion of Adrenal Catecholamine

Catecholamine-secreting tumors that arise from chromaffin cells of the adrenal medulla and the sympathetic ganglia are pheochromocytomas and extraadrenal catecholamine-secreting paragangliomas (extraadrenal pheochromocytomas
Male Reproductive system

The 2 principal functions of the adult male sex organs, the testicles, are the production of sperm and the synthesis of testosterone.

There are three types of cells in the testis:

1. **Leydig cells**; responsible for producing testosterone
2. **Sertoli cells**; help to provide environment needed for spermatogenesis
3. **spermatogonia**; germ cells
Neuroendocrine regulation of testicular function

Testosterone produced by the Leydig cell in response to LH stimulation can inhibit LH release, at the hypothalamus by modulating GnRH release.

The negative feedback inhibition of FSH release occurs at the level of the pituitary and is mainly under regulation by inhibin B, a Sertoli cell–derived peptide.
Testosterone Metabolism

Most of the testosterone released into the circulation is bound to plasma proteins, primarily sex hormone-binding globulin (SHBG) and albumin (44% and 54%, respectively). In the testes, testosterone is bound to androgen-binding protein, a protein with great similarity to SHBG and a product of the same gene. Although SHBG is synthesized predominantly in the liver and released into the systemic circulation, androgen-binding protein is synthesized by Sertoli cells and is released into the lumen of the seminiferous tubules.

At its target cells, testosterone can either have a direct androgen receptor–mediated effect or it can be metabolized to either 17-estradiol through the action of aromatase or to 5-dihydrotestosterone (DHT) through the action of 5-reductase.
Testosterone to Estradiol Conversion

The majority of estradiol in males is produced in adipose tissue through the aromatization of testosterone and, to a smaller extent, of adrenal-derived androstenedione. Some of the 17-estradiol produced in peripheral tissues is released into the circulation, not all estrogens produced from testosterone are involved in mediating endocrine responses. In the liver, testosterone is converted to androstenedione, which is then reduced and conjugated (glucuronidation) to form 17-ketosteroids. The excretion of testosterone and its metabolites in the urine is about 50% in the form of 17-ketosteroids and 50% in the form of polar metabolites such as -diols, -triols, and conjugated forms.
Testosterone to DHT Conversion

The conversion of testosterone to DHT in peripheral tissues, particularly in the skin, produces the most potent natural androgen. The enzymatic conversion of testosterone to DHT is irreversible.

![Metabolism of Testosterone to 5α Dihydrotestosterone](image)
Androgen Receptor-Mediated Physiologic Effects

Both testosterone and DHT bind to identical androgen receptors on their target cells. The androgen receptor is a member of the nuclear receptor superfamily and, like all other nuclear receptors, it consists of 3 functional domains involved in transcriptional regulation, DNA binding, and ligand binding. The ligand-free inactive cytosolic receptor is an inactive oligomer complexed to heat-shock proteins. The oligomeric complex dissociates following hormone binding, undergoes a conformational change, and translocates into the nucleus. In the nucleus, it binds as a homodimer to DNA androgen response elements in the promotor region of target genes and functions as a nuclear transcription factor influencing the transcription of target genes and mediating androgen action.
Physiological effect of androgens

Testosterone controls sexual differentiation (development of the Wolffian ducts), libido (the biologic need for sexual activity and sexual function), pubertal growth of the larynx, anabolic effects in muscle, and stimulation of spermatogenesis.

In contrast, DHT plays a major role in embryonic and pubertal external virilization (eg, development of male external genitalia, urethra, and prostate, and growth of facial and body hair) and contributes to male-pattern balding in individuals with a genetic predisposition for baldness.
Anabolic & Metabolic Effects of Androgens

- In bone, the main physiologic effect of testosterone is to reduce bone resorption.
- Testosterone increases osteoblast lifespan and proliferation.
- It stimulates chondrogenesis in the epiphysial growth plate, increasing pubertal linear growth.
- At puberty, estrogen promotes skeletal maturation and the gradual, progressive closure of the epiphysial growth plate and the termination of chondrogenesis.
- In the adult, estrogen is important in maintaining the constancy of bone mass through its effects on remodeling and bone turnover.
- Increases protein synthesis and decreases protein breakdown, having an overall anabolic effect in muscle.
- Inhibits lipid uptake and lipoprotein lipase activity in adipocytes, stimulates lipolysis by increasing the number of lipolytic -adrenergic receptors, and inhibits differentiation of adipocyte precursor cells.

DHEA stimulates resting metabolic rate and lipid oxidation and enhances glucose disposal by increasing the expression of glucose transporters on the plasma membrane of adipocytes.
Female reproductive system

Uterus and Uterine tubes

- Infundibulum
- Fundus
- Uterus
- Endometrium
- Myometrium
- Perimetrium
- Cervix
- Ovary
- Vagina

Fallopian tubes
Ovarian hormone synthesis

Ovarian production of steroid hormones (progesterone, estrogen, and testosterone) and peptide hormones (inhibins) varies throughout the ovarian cycle.

**Estrogen**: In the ovary, estradiol is formed from the conversion of testosterone into estradiol by the enzyme *cytochrome P450 aromatase*. This occurs in granulosa cells. However, granulosa cells do not have the enzyme 17α-hydroxylase/lyase, and thus cannot convert progesterone into androgens. Where do the androgens required for estrogen production in granulosa cells come from?
Two cell theory of estrogen synthesis

Numerous studies have now shown that the androgens required for aromatization come from the neighboring theca cells:
Ovarian hormones

**Androgens:** Female androgens are derived from the adrenal glands (dehydroepiandrosterone and androstenedione), from the ovaries (androstenedione and testosterone), and from peripheral conversion of androstenedione and dehydroepiandrosterone to testosterone

**Progesterone:** The preovulatory LH surge results in luteinization of granulosa and theca cells, altering the steroidogenic pathway so that progesterone is the primary steroid hormone produced by each of these cell types after luteinization;

**Inhibins, Activins, & Follistatin:** Inhibin production by granulosa cells of mature follicles is regulated by FSH and LH, and locally in an autocrine and paracrine way by growth factors and hormones such as Activin & Follistatin.
From birth, the ovaries of the human female contain about one million of immature oocytes, called **primordial follicles**.

**Primordial follicle**: oocyte surrounded by a single **flat** layer of granulosa cells.

**Primary follicle**: oocyte surrounded by a single **cuboidal** layer of granulosa cells.

**Secondary follicle**: Under hormonal stimulation during puberty, bigger oocyte and several layers of granulosa cells. Formation of theca externa and interna layers from the interstitial tissue surrounding the follicle.
Oogenesis
Graaffian Follicle

is marked by the formation of a fluid-filled cavity adjacent to the oocyte called the antrum. Granulosa and theca cells continue to undergo division concomitant with an increase in antrum volume. Graafian follicles are dependent on the availability of FSH.

Corpus Luteum: After the egg cell has been released, the follicle remains and the granulosa and thecal cells increase in number and becomes known as the corpus luteum. It secretes progesterone and estradiol under the effect of LH. It maintains uterine endometrium in early pregnancy. If fertilization does not occur, it degenerates until it becomes only as scar tissue called corpus albicans.
Menstrual cycle

[Diagram showing the menstrual cycle with labels for ovarian cycle, body temperature, anterior pituitary hormones, ovarian hormones, and uterine cycle. Key stages include growing follicle, ovulation, corpus luteum, corpus albicans, and phases such as follicular phase, luteal phase, and menses.]
Ovarian cycle

1. Follicular Phase: The dominant follicle produces high concentrations of 17-estradiol and inhibin B. As concentrations of estradiol rise, they act on the hypothalamus and pituitary to stimulate low-amplitude, high-frequency pulses (every 90 minutes) of LH, resulting in elevated circulating concentrations of LH that stimulate follicular development, induce ovulation, and decrease FSH secretion at the pituitary level.

2. Luteal Phase;
The surge in LH levels induces ovulation and promotes the survival of the corpus luteum during the luteal phase. Following ovulation, as the corpus luteum develops, high circulating concentrations of progesterone suppress the frequency and the amplitude of LH release, resulting in an overall decrease in LH.

3. Oogenesis & Formation of the Dominant Follicle:

4. Ovulation

5. Formation of the Corpus Luteum

6. Luteolysis
Endometrium cycle: accompanied by ovarian cycle is the cyclic growth and shedding of the lining of the uterus under estrogen and progesterone.

**Proliferative Phase:** This is the initial phase of endometrial maturation in preparation for implantation of the embryo. The preovulatory endometrial proliferation leads to relative hypertrophy of the uterine mucosa.

**Secretory Phase:** This phase corresponds to the ovarian luteal phase and is characterized by progesterone-induced differentiation of the endometrial epithelial cells into secretory cells. During the secretory phase, there is a short, well-defined period of uterine receptivity for embryo implantation.

**Menstrual Phase:** The menstrual period is characterized by shedding of the endometrium, resulting from proteolysis and ischemia in its superficial layer. Proteolytic enzymes accumulate in membrane-bound lysosomes during the first half of the postovulatory period. The integrity of the lysosomal membrane is lost with the decline in estrogen and progesterone on day 25 resulting in lysis of the glandular and stromal cells and the vascular endothelium.
Fertilization

Fertilization is the union of the 2 germ cells, the ovum and the sperm, restoring chromosome number and initiating the development of a new individual. The final steps of mammalian oogenesis (and of spermatogenesis) prepare eggs (and sperm) for fertilization. In preparation for ovulation, fully grown oocytes undergo "meiotic maturation," preparing them to interact with sperm. A very low proportion (approximately 0.002%) of the sperm deposited into the vagina (approximately $10^7$) migrate up the female reproductive tract to the site of fertilization in the ampullary-isthmic junction of the fallopian tubes.

**Implantation:**
The human embryo (blastocyst) enters the uterus 3 days before implantation. As mentioned earlier, the "window of implantation" corresponds to the short period of endometrial receptivity for the embryo, between days 20 and 24 of the menstrual cycle. Outside of this period, implantation fails.
Placental hormones

**Human Chorionic Gonadotropin**

hCG is a heterodimeric glycoprotein from the same hormone family as LH, FSH, and thyroid-stimulating hormone. It is known as the hormone of pregnancy and is the basis for the pregnancy test. hCG is detected in serum at day 6–8 after implantation, and its levels peak at 60–90 days of gestation, declining thereafter. hCG has structural and functional similarity to LH, has a much longer half-life, and exerts its physiologic effects through binding to the LH receptors.

The main function of hCG is to maintain the corpus luteum to ensure the production of progesterone until placental production takes over.

**Human Placental Lactogen and Growth Hormone**

The human growth hormone (hGH) and human placental lactogen (hPL) gene family is important in the regulation of maternal and fetal metabolism and the growth and development of the fetus. hPL is produced by the syncytiotrophoblast and is secreted into both the maternal and fetal circulations after the sixth week of pregnancy.

**Corticotropin-Releasing Hormone**
Placental hormones

**Progesterone**
The major source of progesterone during the initial phase of pregnancy is the corpus luteum under hCG regulation

**Estrogen:** The main source of estrogen during the initial phase of pregnancy is the corpus luteum, being replaced later by placental production

**Corticotrophin-Releasing Hormone:** Play an important role in onset of Labor.
How does birth control work?

1. Interrupts endogenous cycle of estrogens and progesterone.
2. Continuous dosing of estrogens & progesterone leads to feedback inhibition of LH, FSH.
3. No LH surge for ovulation.
4. Progesterone increases the thickness of cervical mucus to prevent sperm swimming upwards.
5. Prevention of follicular maturation and ovulation, not supporting pregnancy.