Chapter 4
Endocrine System

7.1. Endocrine Organs in Man

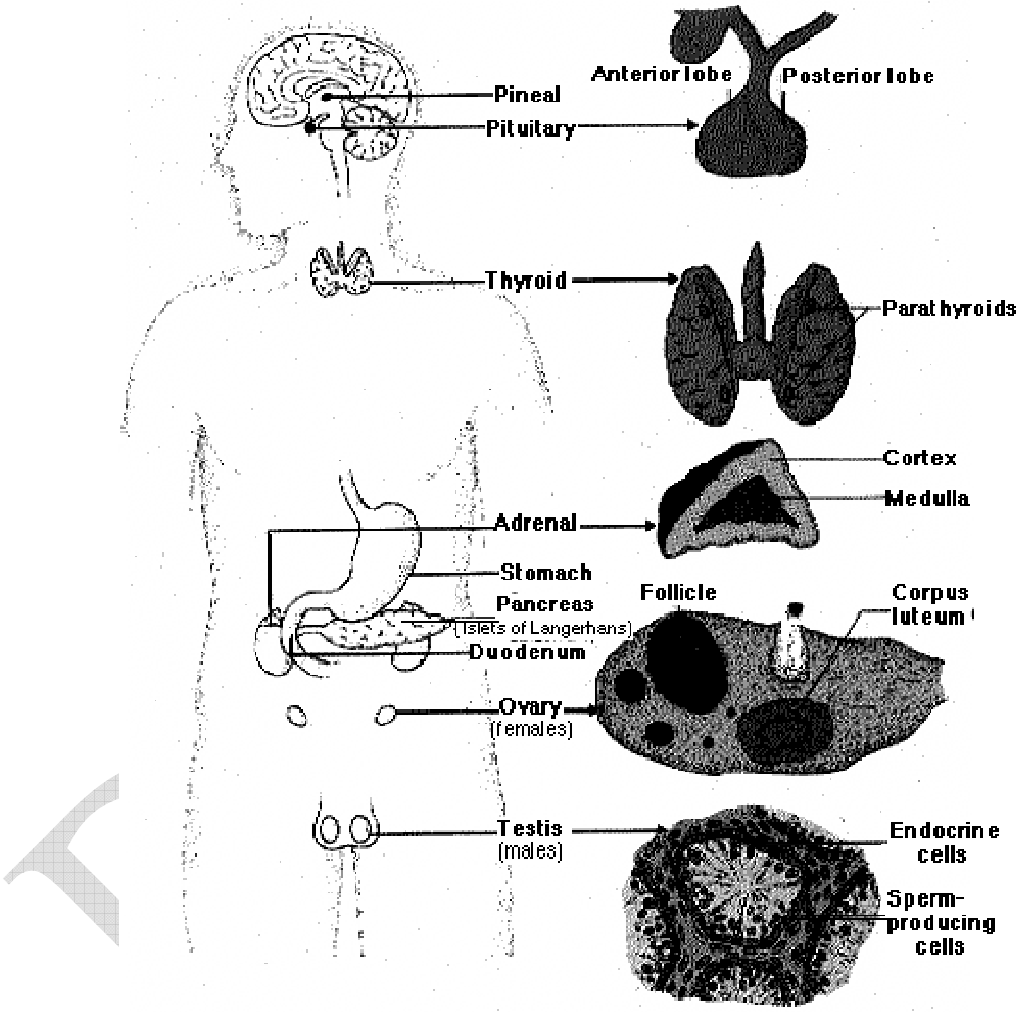


Fig.7.1. Location of Human Endocrine Organs

The essence of multicellularity is the coordinated interaction of the various kinds of cells that make up the body. Cells communicate with each other by chemical signals.

Three kinds of chemical signalling can be distinguished;

- **Autocrine** - the cell signals itself through a chemical that it synthesizes and then responds to. Autocrine signalling can occur
  - solely within the cytoplasm of the cell or
  - by a secreted chemical interacting with receptors on the surface of the same cell
- **Paracrine** - chemical signals that diffuse into the area and interact with receptors on nearby cells. Examples are:
  - The release of **cytokines** that cause an inflammatory response in the area.

- The release of **neurotransmitters** at **synapses** in the nervous system.
- **Endocrine** - the chemicals are secreted into the blood and carried by blood and tissue fluids to the cells they act upon.

This page will examine the properties of endocrine signalling.

7.2. Kinds of Hormones

There are two major classes of hormones: **proteins, peptides, and modified amino acids** and **steroids.**

7.2.1. Proteins, peptides, and modified amino acids

These **hydrophilic** (and mostly large) hormone molecules bind to receptors on the surface of "target" cells; that is, cells able to respond to the presence of the hormone. These receptors are **transmembrane proteins**. Binding of the hormone to its receptor initiates a sequence of intracellular signals that may alter the behaviour of the cell (such as by opening or closing **membrane channels**) or stimulate (or repress) gene expression in the nucleus by turning on (or off) the **promoters** and **enhancers** of the genes.

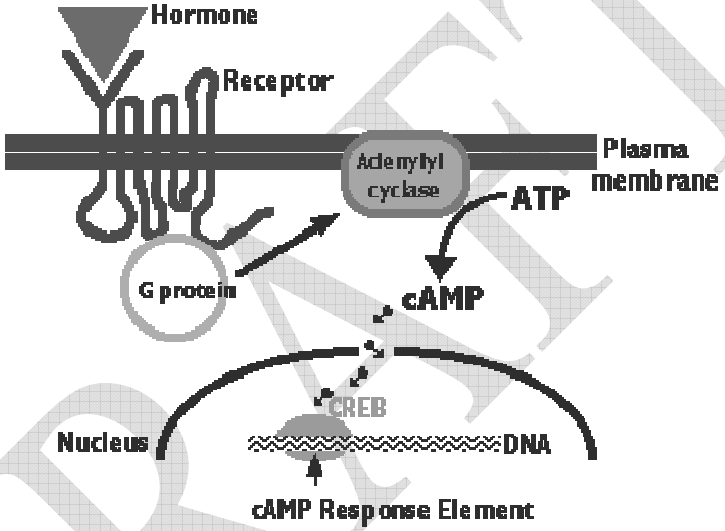


Fig.7.2. Mechanism of action of Proteins, peptides, and modified amino acids hormones

This is the sequence of events: The hormone binds to a site on the extracellular portion of the receptor. The receptors are transmembrane proteins that pass through the plasma membrane 7 times, with their **N-terminal** exposed at the exterior of the cell and their **C-terminal** projecting into the cytoplasm. Binding of the hormone to the receptor activates a **G protein** associated with the cytoplasmic C-terminal. This initiates the production of a **"second messenger"**. The most common of these are **cyclic AMP**, (**cAMP**)which is produced by **adenylyl cyclase** from **ATP**, and **inositol 1,4,5-trisphosphate** (**IP_3**). The second messenger, in turn, initiates a series of intracellular events (shown here as short arrows) such as phosphorylation and activation of enzymes; release of Ca^{2+} into the cytosol from stores within the endoplasmic reticulum. In the case of cAMP, these enzymatic changes activate the **transcription factor CREB** (**c**AMP **r**esponse **e**lement **b**inding protein). Bound to its **response element** 5' TGACGTCA 3' in the promoters of genes that are able to respond to the hormone, activated CREB turns on gene **transcription.** The cell begins to produce the appropriate gene products in response to the hormonal signal it had received at its surface.

7.2.2. Steroid Hormones

Steroid hormones, being **hydrophobic** molecules, diffuse freely into all cells. However, their "target" cells contain cytoplasmic and/or nuclear proteins that serve as receptors of the hormone. The hormone binds to the receptor and the complex binds to **hormone response elements** - stretches of DNA within the promoters of

genes responsive to the hormone. The hormone/receptor complex acts as a **transcription factor** turning target genes "on" (or "off").

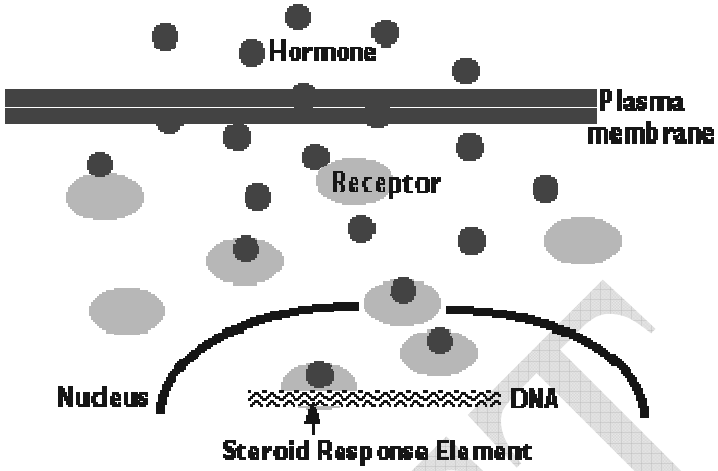


Fig.7.3. Mechanism of Action of Steroid Hormones

Steroid hormone receptors are proteins that have a binding site for a particular **steroid** molecule. Their **response elements are DNA sequences** that are bound by the complex of the steroid bound to its receptor. The response element is part of the **promoter** of a gene. Binding by the receptor activates or represses, as the case may be, the gene controlled by that promoter. It is through this mechanism that **steroid hormones** turn genes on (or off). The glucocorticoid receptor, like all steroid hormone receptors, is a zinc-finger **transcription factor**; the zinc atoms are the four yellow spheres. Each is attached to four cysteines (shown in dark green). For a steroid hormone to turn gene transcription on, its receptor must: bind to the hormone, bind to a second copy of itself to form a **homodimer**, be in the nucleus, moving from the cytosol if necessary, bind to its response element and activate other transcription factors to start **transcription.** Each of these functions depend upon a particular region of the protein (e.g., the zinc fingers for binding DNA). Mutations in any one region may upset the function of that region without necessarily interfering with other functions of the receptor.

7.3. Hormone Regulation

The levels of hormones circulating in the blood are tightly controlled by three **homeostatic** mechanisms:

1. When one hormone stimulates the production of a second, the second suppresses the production of the first.
   Example: The **follicle stimulating hormone** (**FSH**) stimulates the release of estrogens from the ovarian follicle. A high level of estrogen, in turn, suppresses the further production of FSH.
2. Antagonistic pairs of hormones.
   Example: **Insulin** causes the level of blood sugar (glucose) to drop when it has risen. **Glucagon** causes it to rise when it has fallen.
3. Hormone secretion is increased (or decreased) by the same substance whose level is decreased (or increased) by the hormone.
   Example: a rising level of Ca^{2+} in the blood suppresses the production of the **parathyroid hormone** (PTH). A low level of Ca^{2+} stimulates it.

7.4. Hormone Transport

Although a few hormones circulate simply dissolved in the blood, most are carried in the blood bound to **plasma proteins**. For example, all the steroid hormones, being highly hydrophobic, are transported bound to plasma proteins.

7.51. Hormones of the Pituitary

The pituitary gland is pea-sized structure located at the base of the brain. In humans, it consists of two lobes: the **Anterior Lobe** and the **Posterior Lobe**

7.5.1. The Anterior Lobe

The anterior lobe contains six types of secretory cells, all but one of which are specialized to secrete only one of the anterior lobe hormones. All of them secrete their hormone in response to hormones reaching them from the **hypothalamus** of the brain.

(a) Thyroid Stimulating Hormone (TSH)

TSH (also known as thyrotropin) is a **glycoprotein** consisting of: a **beta** chain of 112 amino acids and an **alpha** chain of 89 amino acids. The alpha chain is identical to that found in two other pituitary hormones, **FSH** and **LH** as well as in the hormone **chorionic gonadotropin.** Thus it is its beta chain that gives TSH its unique properties. The secretion of TSH is stimulated by the arrival of **thyrotropin releasing hormone** (**TRH**) from the hypothalamus inhibited by the arrival of **somatostatin** from the hypothalamus. As its name suggests, TSH stimulates the **thyroid gland** to secrete its hormone **thyroxine** ($\mathbf{T_4}$). It does this by binding to transmembrane **G-protein-coupled receptors** (GPCRs) on the surface of the cells of the thyroid.

Some people develop antibodies against their own TSH receptors. When these bind the receptors, they "fool" the cell into making more T_4 causing **hyper**thyroidism. The condition is called **thyrotoxicosis or Graves' disease.**

A deficiency of TSH causes **hypo**thyroidism: inadequate levels of T_4 (and thus of T_3). **Recombinant human TSH** has recently become available to treat patients with TSH deficiency. Some people inherit mutant TSH receptors. This, too, results in hypothyroidism. A deficiency of TSH, or mutant TSH receptors, have also been implicated as a cause of **osteoporosis**. Mice, whose TSH receptors have been knocked out, develop increased numbers of bone-reabsorbing **osteoclasts.**

(b) Follicle-Stimulating Hormone (FSH)

FSH is a **heterodimeric glycoprotein** consisting of the same alpha chain found in TSH (and LH), a beta chain of 115 amino acids, which gives it its unique properties.

Synthesis and release of FSH is triggered by the arrival from the hypothalamus of **gonadotropin-releasing hormone** (**GnRH**). The effect of FSH depends on one's sex

(i) FSH in Females

In sexually-mature females, FSH (assisted by LH) acts on the **follicle** to stimulate it to release **estrogens**.

(ii) FSH in Males

In sexually-mature males, FSH acts on **spermatogonia** stimulating (with the aid of **testosterone**) the production of sperm.

(c) Luteinizing Hormone (LH)

LH is synthesized within the same pituitary cells as FSH and under the same stimulus (**GnRH**). It is also a **heterodimeric glycoprotein** consisting of the same 89-amino acid **alpha** subunit found in FSH and TSH (as well as in **chorionic gonadotropin**); a **beta** chain of 115 amino acids that is responsible for its properties. The effects of LH also depend on sex.

(i) LH in Females

In sexually-mature females, LH stimulates the follicle to secrete **estrogen** in the first half of the menstrual cycle. A surge of LH triggers the completion of **meiosis I** of the egg and its release (**ovulation**) in the middle of the cycle and stimulates the now-empty follicle to develop into the **corpus luteum**, which secretes **progesterone** during the latter half of the menstrual cycle.

(ii) LH in Males

LH acts on the interstitial cells (also known as Leydig cells) of the **testes** stimulating them to synthesize and secrete the male sex hormone, **testosterone**. LH in males is also known as **interstitial cell stimulating hormone** (**ICSH**).

(d) Prolactin (PRL)

Prolactin is a protein of 198 amino acids. During pregnancy it helps in the preparation of the breasts for future milk production. After birth, prolactin promotes the synthesis of milk. Prolactin secretion is stimulated by **TRH** and repressed by **estrogens** and **dopamine**.

In pregnant mice, prolactin stimulates the growth of new neurons in the **olfactory centre** of the brain.

(e) Growth Hormone (GH)

Human growth hormone (also called **somatotropin**) is a protein of 191 amino acids. The GH-secreting cells are stimulated to synthesize and release GH by the intermittent arrival of **growth hormone releasing hormone** (**GHRH**) from the hypothalamus. GH promotes body growth by binding to receptors on the surface of liver cells. This stimulates them to release **insulin-like growth factor-1** (**IGF-1**; also known as **somatomedin**). IGF-1 acts directly on the ends of the long bones promoting their growth

Things that can go wrong due to GH are. In childhood, **hypo**secretion of GH produces the stunted — but normally well-proportioned — growth of a **midget**. Growth retardation can also result from an inability to **respond** to GH. This can be caused by inheriting two mutant genes encoding the **receptors** for **GHRH** or **GH** or homozygosity for a disabling mutation in ***STAT5b***, which is part of the "downstream" signalling process after GH binds its receptor. **Hyper**secretion leads to **gigantism.** In adults, a **hyper**secretion of GH leads to **acromegaly**.

In Hormone-replacement therapy, GH from domestic mammals like cows and pigs does not work in humans. So for many years, the only source of GH for therapy was that extracted from the glands of human cadavers. But this supply was shut off when several patients died from a rare neurological disease attributed to contaminated glands. Now, thanks to recombinant DNA technology, recombinant human GH (rHGH) is available. While a great benefit to patients suffering from GH deficiency, there has also been pressure to use it to stimulate growth in youngsters who have no deficiency but whose parents want them to grow up tall.

(f) ACTH — Adrenocorticotropic Hormone

ACTH is a peptide of 39 amino acids. It is cut from a larger precursor **proopiomelanocortin** (**POMC**). ACTH acts on the cells of the **adrenal cortex**, stimulating them to produce **glucocorticoids**, like **cortisol**, **mineralocorticoids**, like **aldosterone**, **androgens** (male sex hormones, like **testosterone**. In the foetus, ACTH stimulates the adrenal cortex to synthesize a precursor of estrogen called **dehydroepiandrosterone sulphate** (**DHEA-S**) which helps prepare the mother for giving **birth**. Production of ACTH depends on the intermittent arrival of **corticotropin-releasing hormone** (**CRH**) from the hypothalamus. **Hyper**secretion of ACTH is a frequent cause of **Cushing's disease**.

(g) Alpha Melanocyte-Stimulating Hormone (α-MSH)

Alpha MSH is also a cleavage product of proopiomelanocortin (POMC). In fact, α-MSH is identical to the first 13 amino acids at the amino terminal of ACTH.

7.5.2. The Posterior Lobe

The posterior lobe of the pituitary releases two hormones, both synthesized in the hypothalamus, into the circulation.

(a) Antidiuretic Hormone (ADH)

ADH is a peptide of 9 amino acids. It is also known as **arginine vasopressin**. ADH acts on the collecting ducts of the kidney to facilitate the reabsorption of water into the blood. This it acts to reduce the volume of

urine formed (giving it its name of antidiuretic hormone). A deficiency of ADH or inheritance of mutant genes for its **receptor** (called **V2**) leads to excessive loss of urine, a condition known as **diabetes insipidus**. The most severely-afflicted patients may urinate as much as 30 litres (almost 8 gallons!) of urine each day. The disease is accompanied by terrible thirst, and patients must continually drink water to avoid dangerous dehydration. Another type of receptor for arginine vasopressin (designated **V1a**) is found in the brain, e.g., in voles and mice (rodents) and in **primates** like monkeys and humans.

Male prairie voles (*Microtus pinetorum*) and marmoset monkeys have high levels of the V1a receptor in their brains, and tend to be monogamous, and help with care of their young. Male meadow voles (*Microtus montanus*) and rhesus monkeys have lower levels of the V1a receptor in their brains, and are promiscuous, and give little or no help with the care of their young.

Meadow voles whose brains have been injected with a **vector** causing increased expression of the V1a receptor become more like prairie voles in their behaviour. The level of expression of the V1a receptor gene is controlled by a "microsatellite" region upstream (5') of the **ORF**. This region contains from 178 to 190 copies of a repeated tetranucleotide (e.g., CAGA). Prairie voles have more copies of the repeat than meadow voles, and they express higher levels of the receptor in the parts of the brain associated with these behaviours. A similar microsatellite region is present in the **pygmy chimpanzee o**r bonobo (*Pan paniscus*) but is much shorter in the less-affectionate common chimpanzee (*Pan troglodytes*). Changes in the regulatory region of the human gene for the V1a receptor have been linked to autism.

(b) Oxytocin

Oxytocin is a peptide of 9 amino acids. It acts on certain smooth muscles stimulating contractions of the uterus at the time of **birth**; stimulating release of milk when the baby begins to suckle. Oxytocin is often given to prospective mothers to hasten birth. Oxytocin also acts on the nucleus accumbens and amygdala in the brain where it enhances bonding between males and females after they have mated; bonding between a mother and her newborn; and, in humans, increases the level of one's trust in other people.

7.6. Thyroid and Parathyroids

The thyroid gland is a double-lobed structure located in the neck. Embedded in its rear surface are the four parathyroid glands.

7.6.1. The Thyroid Gland

The thyroid gland synthesizes and secretes **thyroxine** (**T_4**) and **calcitonin** T_4 and T_3

Thyroxine (T_4) is a derivative of the amino acid **tyrosine** with four atoms of **iodine**. In target cells (e.g. liver cells), one atom of iodine is removed from T_4 converting it into **triiodothyronine** (**T_3**). **T_3** is the **active hormone**. It has many effects. Among the most prominent of these are: an increase in metabolic rate (seen by a rise in the uptake of oxygen); and an increase in the rate and strength of the heart beat. The thyroid cells responsible for the synthesis of T_4 take up circulating iodine from the blood. This action, as well as the synthesis of the hormones, is stimulated by the binding of **TSH** to **transmembrane receptors** at the cell surface.

(a) Diseases of the Thyroid

(i) Hypothyroid Diseases; caused by inadequate production of T_3

- **Cretinism**: hypothyroidism in infancy and childhood leads to stunted growth and intelligence. Can be corrected by giving thyroxine if started early enough.
- **Myxedema**: hypothyroidism in adults leads to lowered metabolic rate and vigour. Corrected by giving thyroxine.
- **Goiter**: enlargement of the thyroid gland. Can be caused by:
  - inadequate iodine in the diet with resulting low levels of T_4 and T_3;

- an **autoimmune attack** against components of the thyroid gland (called **Hashimoto's thyroiditis**).

Why should a **hypo**thyroid disease produce an enlarged gland? The activity of the thyroid is under negative feedback control:

- the synthesis and release of TRH and TSH is normally inhibited as the levels of T_4 and T_3 rise in the blood.
- When the iodine supply is inadequate, T_4 and T_3 levels fall
- this stimulates the **hypothalamus** and **pituitary** to **increased** TRH and TSH activity respectively. This stimulates the thyroid gland to enlarge (fruitlessly).

- The symptoms of hypothyroidism can also result from **inherited mutations** in the genes encoding:
  - the **receptor for TSH** (present on the surface of thyroid cells) or
  - the **receptor for T_3** (present in the nucleus of almost all cells)

The T_3 receptor is a nuclear protein bound to the **thyroid response element** in the **promoters** of the many genes whose expression is influenced by thyroid hormones. When its ligand, T_3, binds to it, it becomes a **transcription factor** turning on the transcription of many genes.

(ii) hyperthyroid diseases; caused by excessive secretion of thyroid hormones

Graves´ disease. Autoantibodies against the TSH receptor bind to the receptor mimicking the effect of TSH binding. Result: excessive production of thyroid hormones. Graves´ disease is an example of an **autoimmune disease**.

Osteoporosis. High levels of thyroid hormones suppress the production of TSH through the negative-feedback mechanism mentioned above. The resulting low level of TSH causes an increase in the numbers of bone-reabsorbing **osteoclasts** resulting in osteoporosis.

(b) Calcitonin

Calcitonin is a polypeptide of 32 amino acids. The thyroid cells in which it is synthesized have receptors that bind calcium ions (Ca^{2+}) circulating in the blood. These cells monitor the level of circulating Ca^{2+}. A rise in its level stimulates the cells to release calcitonin. Bone cells respond by removing Ca^{2+} from the blood and storing it in the bone. Kidney cells respond by increasing the excretion of Ca^{2+}. Both types of cells have surface receptors for calcitonin. Because it promotes the transfer of Ca^{2+} to bones, calcitonin has been examined as a possible treatment for **osteoporosis**, a weakening of the bones that is a leading cause of hip and other bone fractures in the elderly. Being a polypeptide, calcitonin cannot be given by mouth (it would be digested), and giving by injection is not appealing. However, inhaling calcitonin appears to be an effective way to get therapeutic levels of the hormone into the blood. A synthetic version of calcitonin (trade name = Miacalcin) is now available as a nasal spray.

7.6.2. Parathyroid Glands

The parathyroid glands are 4 tiny structures embedded in the rear surface of the thyroid gland. They secrete **parathyroid hormone** (**PTH**) a polypeptide of 84 amino acids. PTH increases the concentration of Ca^{2+} in the blood in three ways. PTH promotes release of Ca^{2+} from the huge reservoir in the bones. (99% of the calcium in the body is incorporated in our bones.) reabsorption of Ca^{2+} from the fluid in the **tubules in the kidneys**. Absorption of Ca^{2+} from the contents of the intestine (this action is mediated by **calcitriol**, the active form of **vitamin D**.). PTH also regulates the level of phosphate in the blood. Secretion of PTH reduces the efficiency with which phosphate is reclaimed in the **proximal tubules of the kidney** causing a drop in the phosphate concentration of the blood.

(a) Control of the Parathyroids: the Calcium Receptor

The cells of the parathyroid glands have surface **G-protein-coupled receptors** that bind Ca^{2+} (the same type of receptor is found on the calcitonin-secreting cells of the thyroid and on the calcium absorbing cells of the

kidneys). Binding of Ca^{2+} to this receptor **depresses** the secretion of PTH and thus leads to a lowering of the concentration of Ca^{2+} in the blood. Two classes of inherited disorders involving mutant genes encoding the Ca^{2+} receptor occur:

- **Loss-of-function mutations** with the mutant receptor always "off". Patients with this disorder have high levels of Ca^{2+} in their blood and excrete small amounts of Ca^{2+} in their urine. This causes **hyper**parathyroidism.
- **Gain-of-function mutations** with the mutant receptor always "on" (as though it had bound Ca^{2+}). People with this disorder have low levels of Ca^{2+} in their blood and excrete large amounts of Ca^{2+} in their urine. This causes **hypo**parathyroidism.

Rare **autoimmune disorders** can mimic one or the other of these inherited disorders. In each case, **autoantibodies** bind to the receptors.

- If these **inhibit** the receptors, they cause **hyper**parathyroidism.
- If they **activate** the receptors (like those in **Graves' disease**), they cause **hypo**parathyroidism.

(b) Hyperparathyroidism

Tumours in the parathyroids elevate the level of PTH causing a rise in the level of blood Ca^{2+} at the expense of calcium stores in the bones. So much calcium may be withdrawn from the bones that they become brittle and break. Until recently, treatment has been the removal of most — but not all — of the parathyroid tissue (i.e. the goal is the removal of 3 1/2 glands). Now clinical trials have begun on a drug (designated R-568) that mimics the action of calcium on the parathyroids, resulting in a drop in PTH and blood Ca^{2+} and sparing the calcium stores in the bone.

(c) Hypoparathyroidism

Causes:

1. accidental removal of or damage to the parathyroids during neck surgery
2. inherited mutations in the PTH gene
3. inherited predisposition to an autoimmune attack against the parathyroids (and other glands)
4. inherited defect in the embryonic development of the parathyroids (DiGeorge syndrome)

Treatment:

1. give **calcium** supplements
2. give calcitriol 1,25$[OH]_2$ vitamin D_3
3. give teriparatide (Forteo®), a synthetic (by **recombinant DNA**) version of PTH (containing only the 34 amino acids at the **N-terminal**). When given in daily injections it promotes strong bones and thus has been approved as a treatment for **osteoporosis.** While continuous high levels of PTH weaken bones by removing calcium from them, periodic injections of this drug strengthen bone by increasing the number and activity of **osteoblasts.**

7.7. The Adrenal Glands

The adrenal glands are two small structures situated one atop each kidney. Both in anatomy and in function, they consist of two distinct regions: an outer layer, the **adrenal cortex**, which surrounds the **adrenal medulla**.

7.7.1. The Adrenal Cortex

Using **cholesterol** as the starting material, the cells of the adrenal cortex secrete a variety of **steroid** hormones. These fall into three classes: **glucocorticoids** (e.g., cortisol), **mineralocorticoids** (e.g., aldosterone) and **androgens** (e.g., testosterone)

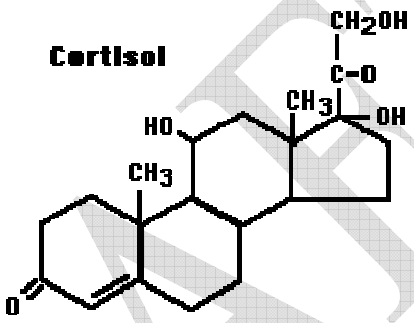
Production of all three classes is triggered by the secretion of **ACTH** from the anterior lobe of the pituitary.

These hormones achieve their effects by travelling through the body in the blood. Because they are so hydrophobic, they must be carried bound to a **serum globulin,** entering from the blood into all cells and

binding to their **receptor** — a protein present in the cytoplasm and/or nucleus of "target" cells. The hormone-receptor complex binds to a second to form a **dimer**. The dimer migrates into the nucleus (if it did not form there). The hormone-receptor dimer binds to specific **hormone response elements** in DNA. These are specific DNA sequences in the **promoter** of genes that will be turned on (sometimes off) by the interaction. Other **transcription factors** are recruited to the promoter and **gene transcription** begins.

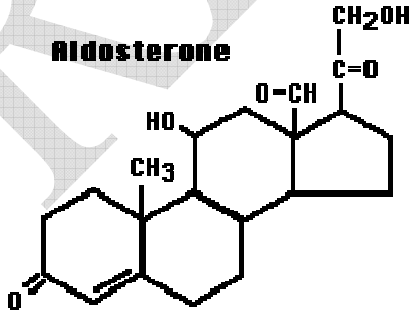
(a) Glucocorticoids

The glucocorticoids get their name from their effect of raising the level of blood sugar (glucose). One way they do this is by stimulating **gluconeogenesis** in the liver: the conversion of fat and protein into **intermediate metabolites** that are ultimately converted into glucose. The most abundant glucocorticoid is **cortisol** (also called hydrocortisone). Cortisol and the other glucocorticoids also have a potent anti-inflammatory effect on the body. They depress the immune response, especially **cell-mediated immune responses.** For this reason glucocorticoids are widely used in therapy: to reduce the **inflammatory** destruction of rheumatoid arthritis and other **autoimmune diseases**, to prevent the **rejection of transplanted organs** and to control **asthma.**



(b) Mineralocorticoids

The mineralocorticoids get their name from their effect on mineral metabolism. The most important of them is the steroid **aldosterone**.

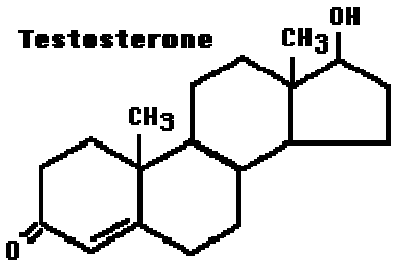


Aldosterone acts on the kidney promoting the reabsorption of sodium ions (Na^+) into the blood. Water follows the salt and this helps maintain normal blood pressure.

Aldosterone also acts on sweat glands to reduce the loss of sodium in perspiration; and acts on taste cells to increase the sensitivity of the **taste buds** to sources of sodium. The secretion of aldosterone is stimulated by a drop in the level of sodium ions in the blood; a rise in the level of potassium ions in the blood; **angiotensin II** and **ACTH** (as is that of cortisol)

(c) Androgens

The adrenal cortex secretes precursors to androgens such as **testosterone**.



In sexually-mature males, this source is so much lower than that of the **testes** that it is probably of little physiological significance. However, excessive production of adrenal androgens can cause premature puberty in young boys. In females, the adrenal cortex is a major source of androgens. Their hypersecretion may produce a masculine pattern of body hair and cessation of **menstruation**.

(d) Addison's Disease: Hyposecretion of Adrenal Cortices

Addison's disease has many causes, such as destruction of the adrenal glands by infection; their destruction by an **autoimmune** attack; and an inherited mutation in the ACTH receptor on adrenal cells. The essential role of the adrenal hormones means that a deficiency can be life-threatening. Fortunately, replacement therapy with glucocorticoids and mineralocorticoids can permit a normal life.

(e) Cushing's Syndrome: Excessive levels of Glucocorticoids

In Cushing's syndrome, the level of adrenal hormones, especially of the glucocorticoids, is too high. It can be caused by excessive production of **ACTH** by the anterior lobe of the pituitary; excessive production of adrenal hormones themselves (e.g., because of a tumour), or (quite commonly) as a result of glucocorticoid **therapy for some other disorder** such as **rheumatoid arthritis** or preventing the rejection of an **organ transplant.**

7.7.2. The Adrenal Medulla

The adrenal medulla consists of masses of neurons that are part of the **sympathetic branch** of the **autonomic nervous system**. Instead of releasing their **neurotransmitters** at a **synapse**, these neurons release them into the blood. Thus, although part of the nervous system, the adrenal medulla functions as an endocrine gland. The adrenal medulla releases **adrenaline** (also called epinephrine) and **noradrenaline** (also called norepinephrine). Both are derived from the amino acid **tyrosine**. Release of adrenaline and noradrenaline is triggered by nervous stimulation in response to physical or mental stress. The hormones bind to **adrenergic receptors — transmembrane proteins** in the plasma membrane of many cell types.

Some of the effects are:

1. Increase in the rate and strength of the heartbeat resulting in increased **blood pressure;**
2. Blood shunted from the skin and viscera to the skeletal muscles, coronary arteries, liver, and brain;
3. Rise in blood sugar;
4. Increased metabolic rate;
5. Bronchi dilate;
6. Pupils dilate;
7. Hair stands on end ("gooseflesh" in humans);
8. **Clotting** time of the blood is reduced;
9. Increased ACTH secretion from the anterior lobe of the pituitary.

All of these effects prepare the body to take immediate and vigorous action.

7.8. Hormones of the Pancreas

The bulk of the pancreas is an **exocrine** gland secreting pancreatic fluid into the duodenum after a meal. However, scattered through the pancreas are several hundred thousand clusters of cells called **islets of**

Langerhans. The islets are **endocrine** tissue containing four types of cells. In order of abundance, they are the: **beta** cells, which secrete **insulin** and **amylin**; **alpha** cells, which secrete **glucagon**; **delta** cells, which secrete **somatostatin**, and **gamma** cells, which secrete a polypeptide of unknown function.

(a) Beta Cells

Insulin is a small protein consisting of an alpha chain of 21 amino acids linked by two disulfide (S—S) bridges to a beta chain of 30 amino acids. Beta cells have channels in their plasma membrane that serve as **glucose** detectors. Beta cells secrete insulin in response to a rising level of circulating glucose ("blood sugar").

Insulin affects many organs. It

1. Stimulates **skeletal muscle fibres** to take up glucose and convert it into **glycogen**; and take up amino acids from the blood and convert them into protein.
2. Acts on liver cells stimulating them to take up glucose from the blood and convert it into glycogen while inhibiting production of the enzymes involved in breaking glycogen back down ("**glycogenolysis**") and inhibiting "**gluconeogenesis**"; that is, the conversion of fats and proteins into glucose.
3. Acts on fat (**adipose**) cells to stimulate the uptake of glucose and the synthesis of **fat**.
4. Acts on cells in the **hypothalamus** to reduce appetite.

In each case, insulin triggers these effects by binding to the **insulin receptor** — a **transmembrane protein** embedded in the plasma membrane of the responding cells.

Taken together, all of these actions result in: the storage of the soluble nutrients absorbed from the intestine into insoluble, energy-rich products (glycogen, protein, fat) a drop in the level of blood sugar

(b) Diabetes Mellitus

Diabetes mellitus is an endocrine disorder characterized by many signs and symptoms. Primary among these are:

1. A failure of the **kidney** to reclaim glucose so that glucose spills over into the urine
2. A resulting increase in the volume of urine because of the **osmotic effect** of this glucose (it reduces the return of water to the blood).

Diabetes mellitus is a disorder quite distinct from the similarly-named **diabetes insipidus.** They both result in the production of large amounts of urine (diabetes), but in one the urine is sweet while in the other (caused by ADH deficiency) it is not. Before the days of laboratory tests, a simple taste test ("mellitus" or "insipidus") enabled the doctor to make the correct diagnosis.

There are three categories of diabetes mellitus:

1. **Insulin-Dependent Diabetes Mellitus** (**IDDM**) [also called "**Type 1**" diabetes] and
2. **Non Insulin-Dependent Diabetes Mellitus** (**NIDDM**)["**Type 2**"]
3. Inherited Forms of Diabetes Mellitus

(i) Insulin-Dependent Diabetes Mellitus (IDDM)

IDDM (also called Type 1 diabetes) is characterized by little (hypo) or no circulating insulin; It most commonly appears in childhood and results from destruction of the beta cells of the islets. The destruction results from a cell-mediated **autoimmune attack** against the beta cells.

IDDM is controlled by carefully-regulated injections of insulin. (Insulin cannot be taken by mouth because, being a protein, it would be digested. However, the U.S. FDA has approved [in January 2006] an insulin inhaler that delivers insulin through the lungs and may reduce the number of daily injected doses needed.)

For many years, insulin extracted from the glands of cows and pigs was used. However, pig insulin differs from human insulin by one amino acid; beef insulin by three. Although both work in humans to lower blood

sugar, they are seen by the immune system as "foreign" and induce an antibody response in the patient that blunts their effect and requires higher doses.

Two approaches have been taken to solve this problem:

1. Convert pig insulin into human insulin by removing the one amino acid that distinguishes them and replacing it with the human version. This approach is expensive, so now the favoured approach is to
2. Insert the human gene for insulin into *E. coli* and grow **recombinant human insulin** in culture tanks. Insulin is not a glycoprotein so E. coli is able to manufacture a fully-functional molecule (trade name = Humulin). **Yeast** is also used (trade name = Novolin).
3. Recombinant DNA technology has also made it possible to manufacture slightly-modified forms of human insulin that work faster (Humalog® and NovoLog®) or slower (Lantus®) than regular human insulin.

Injections of insulin must be done carefully. Injections after vigorous exercise or long after a meal may drive the blood sugar level down to a dangerously low value causing an **insulin reaction**. The patient becomes irritable, fatigued, and may lose consciousness. If the patient is still conscious, giving a source of sugar (e.g., candy) by mouth usually solves the problem quickly. Injections of **glucagon** are sometimes used.

(ii) Non Insulin-Dependent Diabetes Mellitus (NIDDM)

Many people develop diabetes mellitus **without** an accompanying drop in insulin levels (at least at first). In many cases, the problem appears to be a failure to express a sufficient number of **glucose transporters** in the plasma membrane (and **T-system**) of their **skeletal muscles**. Normally when insulin binds to its receptor on the cell surface, it initiates a chain of events that leads to the insertion in the plasma membrane of increased numbers of a **transmembrane** glucose transporter.

This transporter forms a channel that permits the **facilitated diffusion** of glucose into the cell. Skeletal muscle is the major "sink" for removing excess glucose from the blood (and converting it into **glycogen**). In NIDDM, the patient's ability to remove glucose from the blood and convert it into glycogen may be only 20% of normal. This is called **insulin resistance**. Curiously, vigorous exercise seems to increase the expression of the glucose transporter (called **GLUT-4**) on skeletal muscle and this may explain why IDDM is more common in people who live sedentary lives.

NIDDM (also called **Type 2** diabetes mellitus) usually strikes in adults and, particularly often, in overweight people. However, over the last few years in the U. S., the incidence of NIDDM in children has grown to the point where they now account for 20% of all newly-diagnosed cases (and, like their adult counterparts, are usually overweight). Several drugs, all of which can be taken by mouth, are useful in restoring better control over blood sugar in patients with NIDDM. However, late in the course of disease, patients may have to begin to take insulin. It is as though after years of pumping out insulin in an effort to overcome the patient's insulin resistance, the beta cells become exhausted.

(iii) Inherited Forms of Diabetes Mellitus

Some cases of diabetes result from mutant genes inherited from one or both parents. Examples:

1. Mutant genes for one or another of the **transcription factors** needed for transcription of the insulin gene (5 mutant versions have been identified).
2. Mutations in one or both copies of the gene encoding the **insulin receptor**. These patients usually have extra-high levels of circulating insulin but defective receptors. The mutant receptors
   a. may fail to be expressed properly at the cell surface or
   b. may fail to transmit an effective signal to the interior of the cell.
3. A mutant version of the gene encoding **glucokinase**, the enzyme that phosphorylates glucose in the first step of **glycolysis.**

4. Mutations in the gene encoding part of **potassium channels** in the plasma membrane of the beta cell. The channels fail to close properly causing the cell to become **hyperpolarized** and blocking insulin secretion.
5. Mutations in several mitochondrial genes which reduce insulin secretion by beta cells. These diseases are inherited from the mother as only her mitochondria survive in the fertilized egg.

While symptoms usually appear in childhood or adolescence, patients with inherited diabetes differ from most children with NIDDM in having a history of diabetes in the family and not being obese.

(iv) Amylin

Amylin is a peptide of 37 amino acids, which is also secreted by the beta cells of the pancreas. Some of its actions: inhibits the secretion of glucagon; slows the emptying of the stomach; and sends a satiety signal to the brain. All of its actions tend to supplement those of insulin, reducing the level of glucose in the blood.

(c) Alpha Cells

The alpha cells of the islets secrete **glucagon**, a polypeptide of 29 amino acids.

Glucagon acts principally on the **liver** where it stimulates the conversion of glycogen into glucose ("**glycogenolysis**") and fat and protein into **intermediate metabolites** that are ultimately converted into glucose ("gluconeogenesis"). In both cases, the glucose is deposited in the blood. Glucagon secretion is stimulated by low levels of glucose in the blood; inhibited by high levels, and by **amylin**. The physiological significance of this is that glucagon functions to maintain a steady level of blood sugar level between meals. Injections of glucagon are sometimes given to diabetics suffering from an insulin reaction in order to speed the return of normal levels of blood sugar.

(d) Delta Cells

The delta cells secrete **somatostatin**. This consists of two polypeptides, one of 14 amino acids and one of 28. Somatostatin has a variety of functions. Taken together, they work to reduce the rate at which food is absorbed from the contents of the intestine. Somatostatin is also secreted by the **hypothalamus** and by the **intestine.** Further information about somatostatin can be found by following the links.

(e) Gamma Cells

The gamma cells of the islets secrete a 36-amino-acid **pancreatic polypeptide**, which reduces appetite.

7.9. Hormones of the Gut

Over two dozen hormones have been identified in various parts of the gastrointestinal system. All of them are peptides. Many of them are also found in other tissues, especially the brain. Many act in a **paracrine** manner as well as being carried in the blood as true hormones. Their importance to health is uncertain as no known deficiency disorders have been found for any of them. We shall look at 8 of them here: **gastrin**, **somatostatin**, **secretin**, **cholecystokinin** (**CCK**), **ghrelin**, **obestatin**, **neuropeptide Y (NPY)** and **peptide YY$_{3-36}$** (**PYY$_{3-36}$**). Three others are discussed elsewhere in this course.

(a) Gastrin

Gastrin is a mixture of several peptides, of which the most active contains 14 amino acids. It is secreted by cells in the stomach and duodenum. It stimulates the **exocrine** cells of the stomach to secrete **gastric juice**, a mixture of **hydrochloric acid** and the proteolytic enzyme **pepsin**.

(b) Somatostatin

This mixture of peptides is secreted by cells in the gastric glands of the stomach and acts on the stomach (thus a **paracrine** effect) where it **inhibits** the release of **gastrin** and hydrochloric acid. The duodenum where it **inhibits** the release of **secretin** and **cholecystokinin**. The pancreas where it **inhibits** the release of **glucagon**.

Taken together, all of these actions lead to a reduction in the rate at which nutrients are absorbed from the contents of the intestine. Somatostatin is also secreted by the **hypothalamus** and the **pancreas.**

(c) Secretin

It is a polypeptide of 27 amino acids. It is secreted by cells in the duodenum when they are exposed to the acidic contents of the emptying stomach. It stimulates the exocrine portion of the **pancreas** to secrete **bicarbonate** into the **pancreatic fluid** (thus neutralizing the acidity of the intestinal contents).

(d) Cholecystokinin (CCK)

CCK is a mixture of peptides, of which an octapeptide (8 amino acids) is the most active. It is secreted by cells in the duodenum and jejunum when they are exposed to food. It acts on the **gall bladder** stimulating it to contract and force its contents of **bile** into the intestine and on the **pancreas** stimulating the release of **pancreatic digestive enzymes** into the pancreatic fluid. CCK also acts on **vagal neurons** leading back to the **medulla oblongata** which give a **satiety signal** (i.e., "that's enough food for now").

(e) Ghrelin and Obestatin

(i) Ghrelin

This peptide of 28 amino acids is secreted by endocrine cells in the stomach, especially when one is hungry; It acts on the hypothalamus to **stimulate** feeding; This action counteracts the inhibition of feeding by **leptin, PYY_{3-36},** and obestatin.

(ii) Obestatin

This peptide of 23 amino acids is cut from the same precursor molecule from which ghrelin is generated. But its effects — at least in rats and mice — are just the reverse of those of ghrelin.

Effects on	Ghreli	Obestatin
food intake	↑	↓
emptying of the stomach	↑	↓
peristalsis in the intestine	↑	↓
body weight	↑	↓

Presumably, the cutting of each precursor molecule (a peptide of 117 amino acids) yields one molecule of each hormone so one might expect their effects to cancel out. However, each hormone must receive further chemical modification to be active and perhaps controlling this permits one or the other to dominate under the appropriate conditions.

(f) Neuropeptide Y (NPY)

Neuropeptide Y (which is also secreted by neurons in the hypothalamus) contains 36 amino acids. It is a potent feeding **stimulant** and causes increased storage of ingested food as fat. Neuropeptide Y also blocks the transmission of **pain** signals to the brain.

(g) PYY_{3-36}

Peptide YY_{3-36} contains 34 amino acids, many of them in the same positions as those in neuropeptide Y. But the action of PYY_{3-36} is just the reverse of that of NPY, being a potent feeding **inhibitor**. It is released by cells in the intestine after meals. The amount secreted increases with the number of calories that were ingested. PYY_{3-36} acts on the hypothalamus to suppress appetite; the **pancreas** to increase its exocrine secretion of digestive juices; and on the **gall bladder** to stimulate the release of bile. The appetite suppression mediated by PYY_{3-36} works more slowly than that of **cholecystokinin** and more rapidly than that of **leptin**. In a recent human study, volunteers given PYY_{3-36} were less hungry and ate less food over the next 12 hours than those who received saline (neither group knew what they were getting).

The endocrine cells of the small intestine also secrete **serotonin** and **substance P.**

7.10. Hormones of the Liver

The liver synthesizes and secretes at least three important hormones: These are **Insulin-like Growth Factor-1** (**IGF-1**), **Angiotensinogen** and **Thrombopoietin**

7.10.1. Insulin-like Growth Factor-1

This protein of 70 amino acids was once called **somatomedin** because it, not **growth hormone,** is the immediate stimulus for growth of the body. Growth hormone released from the anterior lobe of the pituitary. It binds to receptors on the surface of liver cells which and stimulates the synthesis and release of IGF-1 from them. Many cells have **receptors** for IGF-1, especially cells in the bone marrow and in the cartilaginous growing regions of the long bones. Binding of IGF-1 to cells with receptors for it stimulates them to move from G_1 of the **cell cycle** to S phase and on to mitosis.

7.10.2. Angiotensinogen

This protein is released into the blood where it serves as the precursor for **angiotensin**. How angiotensin is manufactured, and the role it plays in maintaining blood pressure is described in the discussion of renin.

7.10.3. Thrombopoietin (TPO)

Thrombopoietin is a protein of 332 amino acids. It stimulates precursor cells in the bone marrow to differentiate into **megakaryocytes**. Megakaryocytes generate **platelets**, essential to **blood clotting**. The production of megakaryocytes — and thus platelets — is under homeostatic control. It works like this: Circulating platelets are covered with receptors for TPO. So are megakaryocytes and their precursors, but there are fewer of them. When platelet counts are high, most of the circulating TPO is bound to the platelets and less is left to stimulate megakaryocytes. When platelet counts drop, more TPO becomes available to stimulate megakaryocytes to replenish the platelet supply.

7.11. Hormones of the Skin

When **ultraviolet radiation** strikes the skin, it triggers the conversion of dehydrocholesterol (a **cholesterol** derivative) into **calciferol** (vitamin D_3). Calciferol travels in the blood to the liver where it is converted into 25[OH] vitamin D_3. This compound travels to the kidneys where it is converted into **calcitriol** (1,25 $[OH]_2$ vitamin D_3). This final step is promoted by the **parathyroid hormone** (PTH). Although called a vitamin, calciferol and its products fully qualify as hormones because they are made in certain cells, carried in the blood, and affect gene transcription in target cells.

7.12. Hormones of the Heart

In response to a rise in **blood pressure**, the heart releases two peptides:

- **A-type Natriuretic Peptide** (ANP)

This hormone of 28 amino acids is released from stretched **atria** (hence the "A").

- **B-type Natriuretic Peptide** (BNP)

This hormone (29 amino acids) is released from the **ventricles**. (It was first discovered in brain tissue; hence the "B".)

Both hormones lower blood pressure by **relaxing arterioles,** inhibiting the secretion of **renin** and **aldosterone**, inhibiting the reabsorption of sodium ions by the kidneys.

The latter two effects reduce the reabsorption of water by the kidneys. So the volume of urine increases as does the amount of sodium excreted in it. The net effect of these actions is to reduce blood pressure by reducing the volume of blood in the circulatory system. These effects give ANP and BNP their name (natrium = sodium; uresis = urinate).

7.13. Melatonin and the Pineal Gland

The pineal gland is a tiny structure located at the base of the brain. Its principal hormone is **melatonin**, a derivative of the amino acid **tryptophan**. Synthesis and release of melatonin is **stimulated by darkness** and **inhibited by light**. But even without visual cues, the level of melatonin in the blood rises and falls on a daily (**circadian**) cycle with peak levels occurring in the wee hours of the morning.

However, this cycle tends to drift in people who are totally blind - often making them sleepy during the day and wide awake at night. Giving melatonin at bedtime has proved helpful in a number of cases.

Melatonin is readily available in drug stores and health food stores, and it has become quite popular. Ingesting even modest doses of melatonin raises the melatonin level in the blood to as much as 100 times greater than normal. These levels appear: to promote going to sleep and thus help insomnia, to hasten recovery from jet lag and not to have dangerous side effects. Its name because of its effect on melanocytes: skin cells that contain the black pigment, **melanin**. In humans, melanocytes are responsible for moles, freckles, and suntan (and, if they turn cancerous, **melanoma**). In most vertebrates, MSH is produced by an intermediate lobe of the **pituitary gland**. Its secretion causes a dramatic darkening of the skin of fishes, amphibians, and reptiles. The darkening occurs as granules of melanin spread through the branches of specialized melanocytes called **melanophores**.

The photomicrograph on the right shows melanophores in the skin of a frog with the melanin dispersed throughout the branches of the cells. This effect is produced by MSH. When the pigment retreats to the center of the cells, the skin lightens. The granules are carried outward along **microtubules** using **kinesin** as the motor. They assemble at the actin-rich periphery of the cell carried by myosin. The granules are carried back to the center of the cell along microtubules using **dynein** as the motor.

The photo below was taken a few moments after the frog on the right was injected with a small dose of MSH. The response to MSH does not occur during mitosis; presumably the microtubules with their dyneins and kinesins are needed for operation of the **mitotic spindle. Proopiomelanocortin** (**POMC**), the same precursor molecule from which the **adrenocorticotropic hormone** (ACTH) is synthesized, also produces two forms of MSH. One of them, **α-MSH**, is identical to the first 13 amino acids at the **amino terminal** of ACTH. α-MSH can cause darkening of human skin. When injected into human bodies α-MSH — also called **Melanotan I** — darkens the skin texture. This raises the possibility of using melanotan to get a suntan without the risks of exposure to ultraviolet light. A second synthetic version of MSH — dubbed Melanotan II — also darkened the skin of male volunteers. Unexpectedly, it also caused penile erections in males. This has raised the possibility of using MSH to cure impotence.

MSH plays a role in appetite. Humans have no intermediate lobe in their pituitary gland, and MSH may not be a circulating hormone for us. However, α-MSH is found in the brain where it acts to suppress appetite. Some cases of extreme obesity have been traced to mutations in the brain receptor for α-MSH. Presumably these people are unable to respond to the appetite-suppressing effect of their α-MSH.

7.14. Leptin

Human leptin is a protein of 167 amino acids. It is manufactured in **fat cells** (**adipose tissue**), and the level of circulating leptin is directly proportional to the total amount of fat in the body. Leptin acts on receptors in the **hypothalamus** of the brain where it:

1. Counteracts the effects of **neuropeptide Y** (a potent feeding stimulant secreted by cells in the gut and in the hypothalamus);
2. Counteracts the effects of **anandamide** (another potent feeding stimulant that binds to the same receptors as **THC**, the active ingredient of marijuana)
3. Promotes the synthesis of **α-MSH**, an appetite suppressant;

The result: inhibition of food intake. This inhibition is long-term, in contrast to the rapid inhibition of eating by **cholecystokinin** (CCK) and the slower suppression of hunger between meals mediated by **PPY_{3-36}.** The absence of a functional hormone (or its receptor) leads to uncontrolled food intake and resulting obesity.
Leptin also acts on hypothalamic neurons responsible for the secretion of **gonadotropin-releasing hormone** (**GnRH**). Women who are very thin from limited food intake or intense physical training may cease to menstruate because of their lack of leptin-secreting fat cells. Treating them with **recombinant human leptin** can sometimes restore normal menstruation. Stimulating the **sympathetic nervous system** to modulate the balance between the formation and breakdown of **bone**.

7.15. Resistin

Fat cells in mice also secrete a small protein (108 amino acids) called resistin. Resistin causes tissues — especially the liver — to be **less sensitive** to the action of **insulin**, which is the hallmark of **Non Insulin-Dependent Diabetes Mellitus (NIDDM)** ("Type 2" diabetes). Blood glucose levels rise because of increased **glycogenolysis** and **gluconeogenesis** in the liver. In humans, resistin is primarily a product of **macrophages,** not fat cells. Nevertheless, there is a strong association in humans between elevated levels of resistin, obesity, and Type 2 diabetes (over 80% of the people with NIDDM are obese).

7.16. Retinol Binding Protein 4 (RBP4)

This protein (of ~180 amino acids) is responsible for the transport of retinol (vitamin A) in the blood. When it is secreted in elevated amounts by fat cells, it suppresses glucose uptake by skeletal muscle; enhances glucose release by the **liver.** Elevated leves of RBP4 occur in humans with **Type 2 diabetes mellitus (NIDDM).**

7.17. Insect Hormones

Because of their rigid exoskeleton, insects can grow only by periodically shedding their exoskeleton - called **molting**. Molting occurs repeatedly during larval development. At the final molt, the adult emerges.

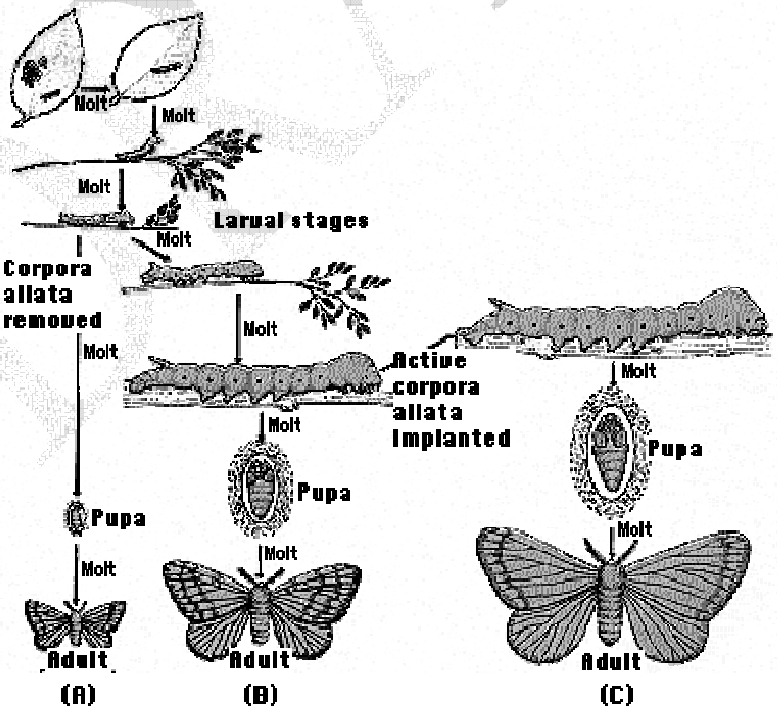


Fig.7.4. Metamorphoses in butterfly

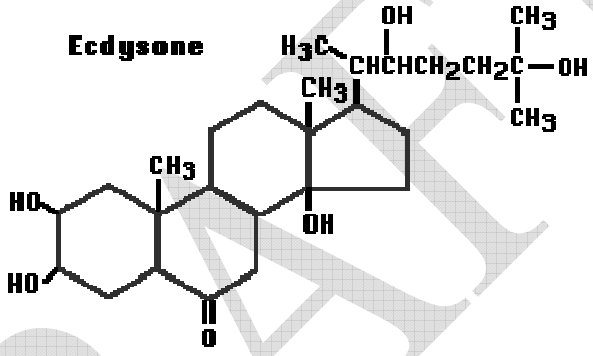
In several insect orders, the adult looks entirely different from the larva that preceded it. This marked transformation is called **metamorphosis**. Metamorphosis takes place during a dormant stage called the **pupa**. The sequence ending in the center panel **(B)** shows the larval, pupal, and adult stages during normal development of the domestic silkworm moth, **Bombyx mori**.

7.17.1. Prothoracicotropic Hormone (PTTH)

Molting and pupation require the hormone, PTTH, secreted by a two pairs of cells in the brain of the larva. If these cells are cut out of the brain of a full-grown larva, pupation does not occur. This is not because of the trauma of surgery; if transplanted somewhere else in the caterpillar's body, pupation occurs normally. PTTH is a homodimer of two polypeptides of 109 amino acids. PTTH does not drive pupation directly but, as its name suggests, acts on the **prothoracic glands**.

7.17.2. Ecdysone

There are two prothoracic glands located in the thorax. Under the influence of PTTH, they secrete the **steroid** hormone **ecdysone**. Acting together, PTTH and ecdysone trigger every molt: larva-to-larva as well as pupa-to-adult. What, then, accounts for the dramatic changes of metamorphosis?



7.17.3. Juvenile Hormone (JH)

Juvenile hormone is secreted by two tiny glands behind the brain, the **corpora allata**.

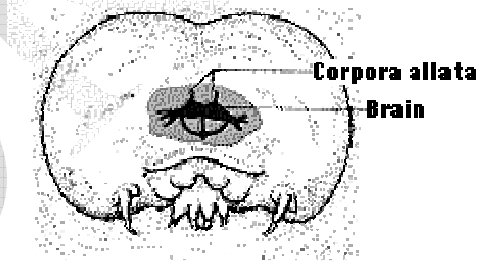


Fig.7.5. Gland of Juvenile Hormone

As long as there is enough JH, ecdysone promotes larva-to-larva molts. With lower amounts of JH, ecdysone promotes pupation. Complete absence of JH results in formation of the adult. So if the corpora allata are removed from an immature silkworm, it immediately spins a cocoon and becomes a small pupa. A miniature adult eventually emerges (shown in **panel (A) above**). Conversely, if the corpora allata of a young silkworm are place in the body of a fully-mature larva, metamorphosis does not occur. The next molt produces an extra-large caterpillar (**panel (C) above**).

Adult insects do not normally molt, but if extra amounts of **PTTH** are given to an adult **Rhodnius** (the "kissing bug"), it is forced into an extra molt. The English insect physiologist V. B. Wigglesworth showed

that if juvenile hormone is first applied to the insect's exoskeleton, the regions affected by it revert to larval type after this extra molt.

7.17.4. Insect Hormones and Pest Control

Knowledge of insect hormones has provided a number of opportunities to enlist them - or molecules related to them - in the battle against insect pests.