Endocrine Physiology Summary

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This summary contains all the information required in the exams.

Sheets 1 and 4 are copied, without changes, to this summary.

The last 9 pages contain 40 suggested multiple choice questions; their answers are in the last page. The first 21 are copied from sheet 5.

Endocrine Physiology

Of all body systems, only 2 control its activities; the **nervous** and the **endocrine** systems

	Endocrine system	**Nervous system**
Signal transfer	Hormones reach the tissues via blood	Neurotransmitters are released from a neuron
Cells affected	Almost all body's cells	Another neuron, a muscle or a gland.
Main effects	Changing metabolic activities	Muscle contraction, secretion of hormones and enzymes
Onset of action	Usually delayed (an exception is epinephrine)	Usually immediate
Duration of action	Long	Short

Types of Glands

- **Exocrine glands:**

  1) Secretions are released into a duct which opens either inside the body such as the intestine or outside the body such as sweat glands.

- **Endocrine glands:**

  1) **Classic endocrine glands: ductless** glands which secrete **classic hormones** into the blood**.**

  2) **Autocrine glands:** hormones released into the interstitial spaces, bind to specific receptor on the cell of origin**.**

  3) **Paracrine glands**: hormones released into the interstitial spaces, bind to specific receptor of nearby cells.

  4) **Neuroendocrine glands:** Secrete **neurohormones :**

     - Into the **blood,** e.g. posterior pituitary**.**
     - Into the **synaptic cleft** affecting the post synaptic neurons, e.g. epinephrine**.**

- **Pheromones:** volatile hormones (evaporate rapidly), released into the environment to act on olfactory cells of another individual, produced by animals to produce physiologic changes in another animal of the same species :
  - In animals, examples include male deer and amber which is produced by whales in their intestines.
  - Also present in humans, especially females. Males and females attract each other "chemistry".

Notes

- Some endocrine glands produce **many** hormones with different control mechanisms and functions.
  - The **anterior pituitary** and the **pancreas** secrete many hormones.

- Most hormones have multiple effects in their target tissues and are said to have **pleotrotropic** effects.
  - This phenomenon occurs when a single hormone regulates several functions in the target tissue.
  - **Insulin** stimulates glucose uptake, glycolysis, and glycogenesis, inhibit glycogenolysis, stimulates amino acids uptake, stimulates protein synthesis and inhibit protein degradation.

- Some hormones affect **more** than one tissue.

- Most cells are affected by **many** hormones.

- The same chemical can be classified as a **hormone** or a **neurotransmitter** depending on the source of secretion; a gland or a hormone and the mode of delivery of the chemical to tissues.
  - When somatostatin is secreted from the hypothalamus it's a neurotransmitter. When it's secreted form the pancreas it's a hormone.

- Some hormones' secretion is stimulated by **different** stimuli to affect the same physiological process.
  - Many hormones including insulin, glucagon, epinephrine, thyroid hormones, and adrenal glucocorticoids may regulate liver glycogen metabolism as responses to different stimuli.

- **Chronic** exposure of a cell to a specific hormone sometimes causes desensitization by reducing the number or the sensitivity of the receptors available to bind the same hormone (**homologous desensitization**) or another hormone (**heterologous desensitization**).
    - The reduction in number is achieved by reducing synthesis or sinking down of the receptors.

- Desensitization is **critical** to life.
- Sometimes, this exposure causes up-regulation of the receptors rather than down-regulation.

Hormones Effects

1) Control **metabolic** activities.
2) Sex hormones are required to produce germ cells and **reproduce**.
3) GI hormones are essential for the **digestive** process.
4) Control **CVS** (cardiac output, blood pressure, blood volume)
5) **Transport** of substances from the blood to cells or vice versa.
6) Affect the **immune** system
7) Growth hormone and others are necessary for normal **growth**.
8) Regulate the response to a **stress**.
9) Affect individual's **behaviors**; male behave differently from females.

Chemical classification of hormones

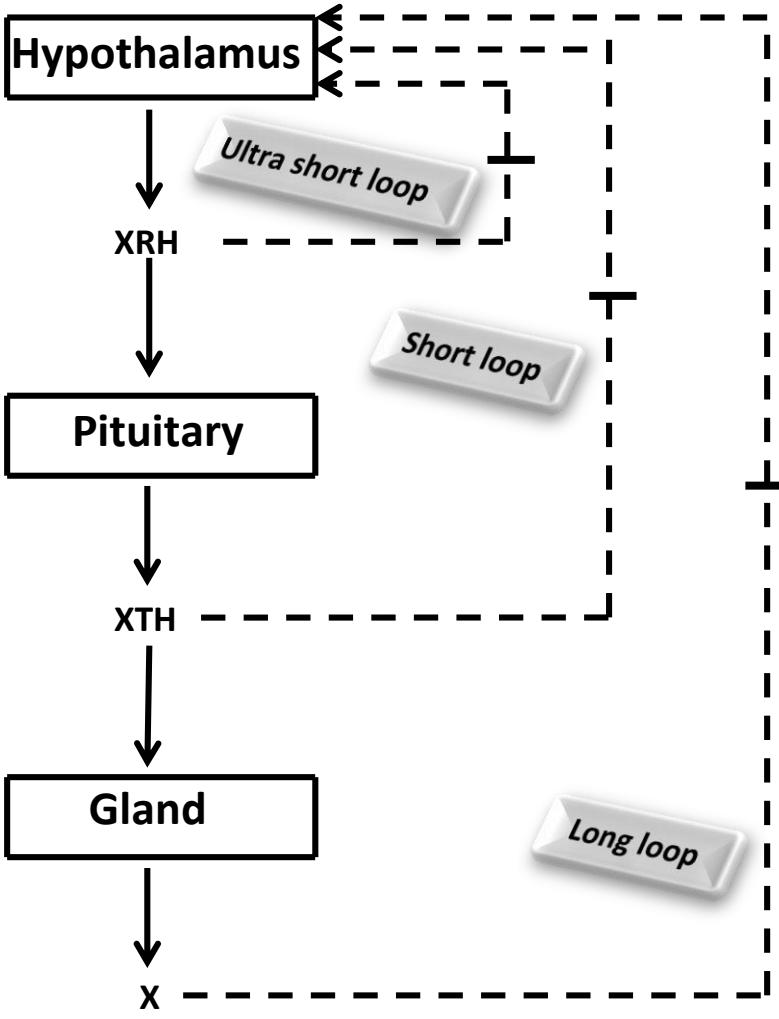
1- **Proteins** (more than 100 amino acids) or **polypeptides** (less than 100 amino acids)
2- **Amino acid** derivatives: catecholamines (epinephrine, norepinephrine, dopamine) and Thyroid hormones (T3,T4).
3- **Steroids**: adrenal cortex hormones and sex hormones.

Regulation of hormone secretion

- The **stimulus – response** could be:
  a) **Hormone - hormone** (the stimulus is a hormone and the response is a hormone)
  b) **Substrate - hormone** e.g. Glucose-insulin
  c) **Mineral – hormone** e.g. Calcium - parathyroid hormone

- **This is achieved by 3 main mechanisms:**

1) **Feedback control:**
    a. **Positive feedback:** The response to the hormone **stimulates** additional secretion of the hormone. Both suckling of milk and uterine contractions stimulate additional oxytocin secretion.
    b. **Negative feedback:** The response to the hormone **inhibits** additional secretion of the hormone.
2) **Neural control:**
    - **Neurons** secrete hormones that modulate hormone secretion in **special** conditions, like pain, emotional or sexual excitement, fright, injury and stress. e.g. adrenalin, acetylcholine, dopamine, serotonin.
3) **Chronotropic control:**
    a. **Diurnal rhythm/ sleep-wake cycle:** the secretion of growth hormone is at its highest at 12 mid-noon and 12 mid-night.
    b. **Menstrual rhythm:** The level of estrogen, progesterone, LH and FSH vary during the 28 days of the menstrual cycle.
    c. **Developmental rhythm**: secretion of growth hormone varies according to the stages of development; childhood, puberty, adulthood, and old age.



As a response to a stimuli, the hypothalamus secretes X releasing hormone (**XRH**)

XRH stimulates the pituitary gland to secrete X tropic hormone (**XTH**)

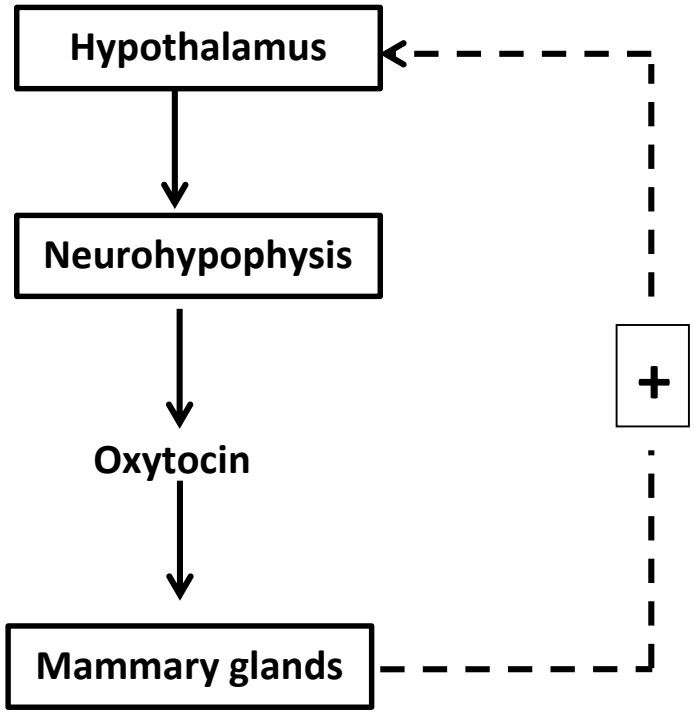
XTH stimulates a peripheral gland to secrete **X** hormone.

X does its physiological effects on many tissues.

In order to stop **additional** X hormone secretion, **negative feedback** mechanism is needed.

Note the 3 forms of the negative feedback

Ultra short loop (autocrine), **short loop**, **long loop**



The hypothalamus stimulates the posterior pituitary (**neurohypophysis**) to secrete oxytocin.

Oxytocin causes the mammary gland to **release** milk.

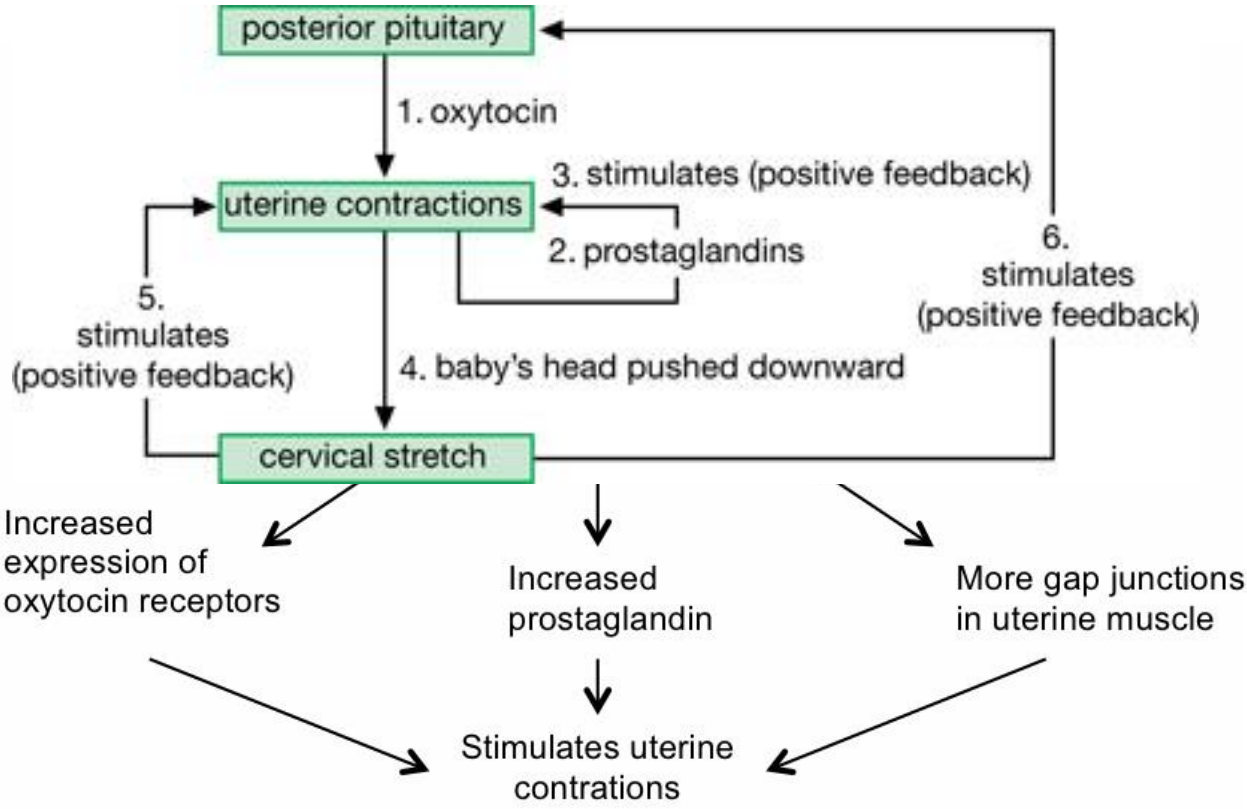
The baby **suckles** the milk.

This suckling stimulates **sensory** neurons to cause **additional** release of oxytocin.

This is called **positive feedback**

During pregnancy, **estrogens** increases **oxytocin receptors** in the **myometrium** which increases uterine resposiveness to the circulating oxytosin (**without** increasing oxytocin concentration) which in turn increases muscle contraction. This only **initiates** paturition.

These contractions push the fetus against the **cervix**. This stimulates **additional** oxytocin secretion from the **posterior** pituitary. Also, oxytocin increases production of **prostaglandins** which, togother with oxytocin, **stimulate** smooth muscle contractions. After delivery, oxytocin level returns back to **normal** and contractions stop.



Hormonal Interactions

1) Permissive effect:

- Thyroxine alone **doesn't** cause fat cells to release fatty acids.
- Epinephrine alone only **slightly** stimulates fat cells to release fatty acids.
- Binding of thyroxine and epinephrine **together** to fat cells **greatly** increases fatty acids release.
- Thyroxine has a **permissive** effect as it **allows** epinephrine to cause an effective response.
- Thyroxine increases the **number** and more **importantly** the **affinity** of the receptors of epinephrine.

- Another example: **estrogens** permit the effects of **progesterone** in prepairing the uterus for **implantation**.

2) **Synergistic effect**:
   - **Each** of the hormones estrogens, progesterone, prolactin and oxytocin, affect mammary glands to secrete milk.
   - For this response to be **effective**, cells require **all** these hormones togother.
3) **Antagonistic effect**:
   - A hormone **opposes** the action of another hormone on the same target cell.
   - Insulin **decreases** blood glucose level. Glucagon **increases** blood glucose level.

Second messenger systems

G protein coupled receptor

- G protein is a **trimer** (3 subunits; α, β, γ). In its inactive form it forms a complex that binds **GDP**. In its active form it binds **GTP** which causes the **α** subunit to dissociate.
- The coupled receptor is a protein of 7 trans-membrane α-helices
- **Catecholamines** and most **peptide hormones** receptors are G protein coupled because such hormones **can't** cross cell **membranes**.

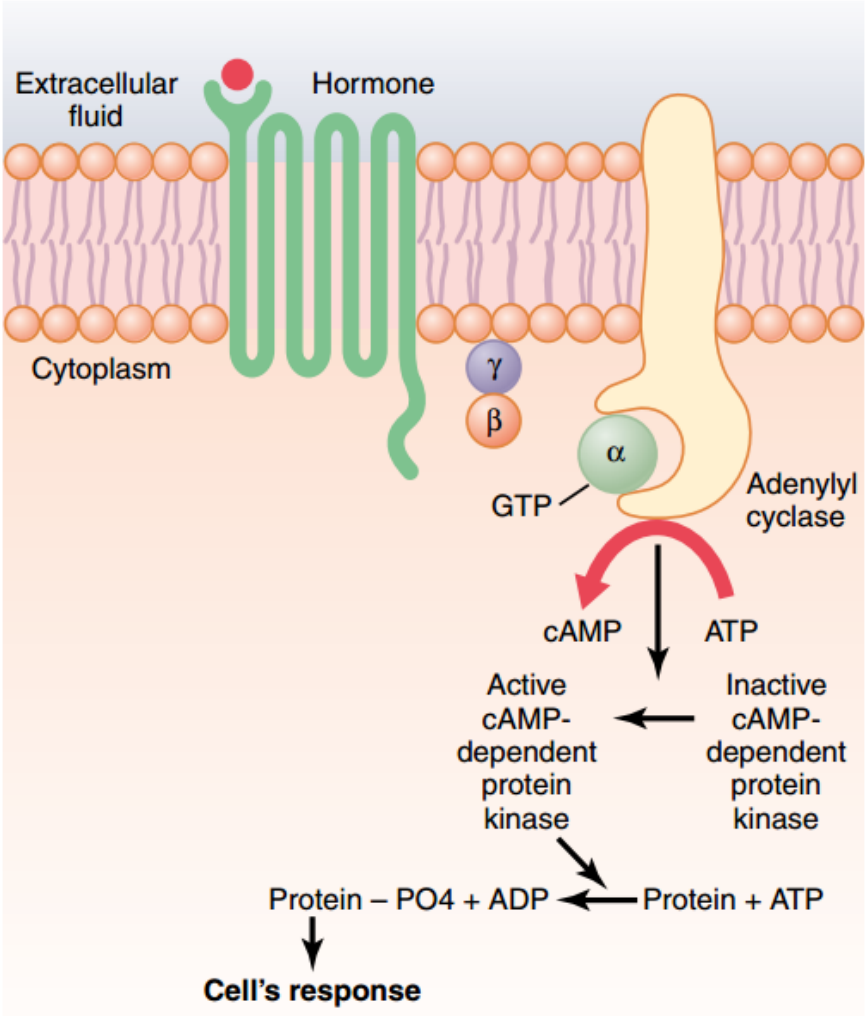
Mechanism of action

G- protein coupled receptor

1) The **hormone** (first messenger) binds to a g protein coupled receptor in the cell membrane.
2) This receptor undergoes a **conformational** change causing the G protein with its all 3 subunits and **GDP** to bind the cytoplasmic part of the receptor.
3) This **GDP** is exchanged with **GTP** causing the α subunit to **dissociate**.
4) The α-subunit **associates** with another protein altering their activity.

- One receptor activates **hundreds** of G protein. Each one activates hundreds of enzymes and so on. This is called signal **amplification**.

1) 3',5'-Cyclic adenosine monophosphate (cAMP)

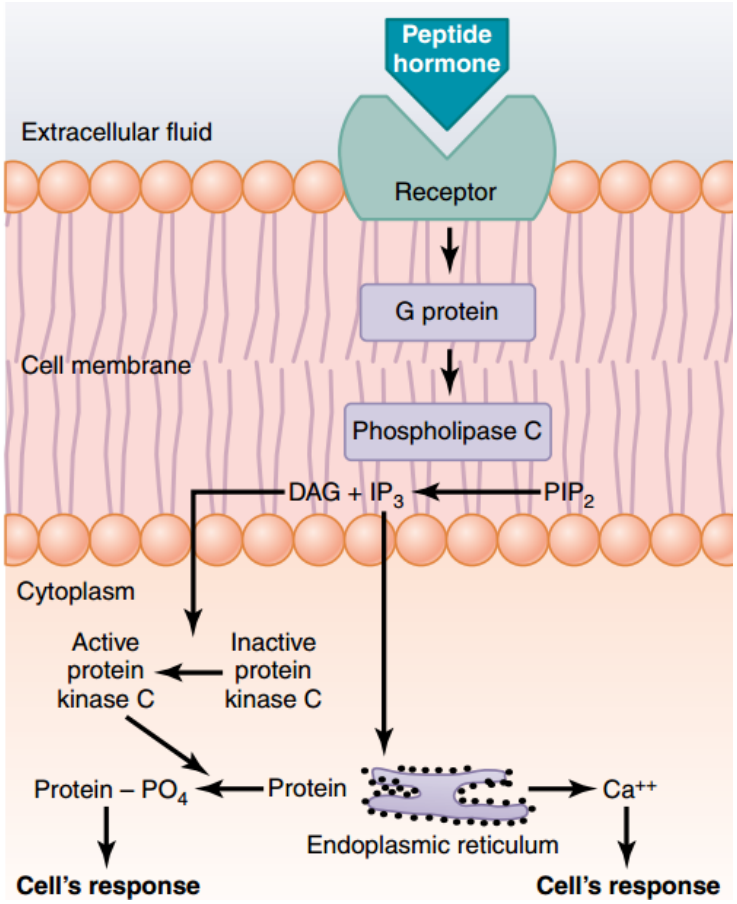


1) The α-subunit binds the enzyme**, adenylyl cyclase**
2) Adenylyl cyclase converts **ATP** to **cAMP**.
3) These cAMP molecules bind to **cAMP-dependent protein kinase** (**protein kinase A**)
4) Protein Kinase A alters the activity of **other enzymes** by **phosphorylation**.
5) To stop the response, the enzyme, **phosphodiestrase** breaks **cAMP** to form **AMP**.

Adrenocorticotropic hormone (ACTH)
Angiotensin II (epithelial cells)
Calcitonin
Catecholamines (β receptors)
Corticotropin-releasing hormone (CRH)
Follicle-stimulating hormone (FSH)
Glucagon
Human chorionic gonadotropin (HCG)
Luteinizing hormone (LH)
Parathyroid hormone (PTH)
Secretin
Somatostatin
Thyroid-stimulating hormone (TSH)
Vasopressin (V_2 receptor, epithelial cells)

Hormones whose effects are mediated by cAMP

2) Calcium ions, Inositol-1,4,5-triphosphate, Diacylglycerol (Ca^{2+}, IP3, DAG)



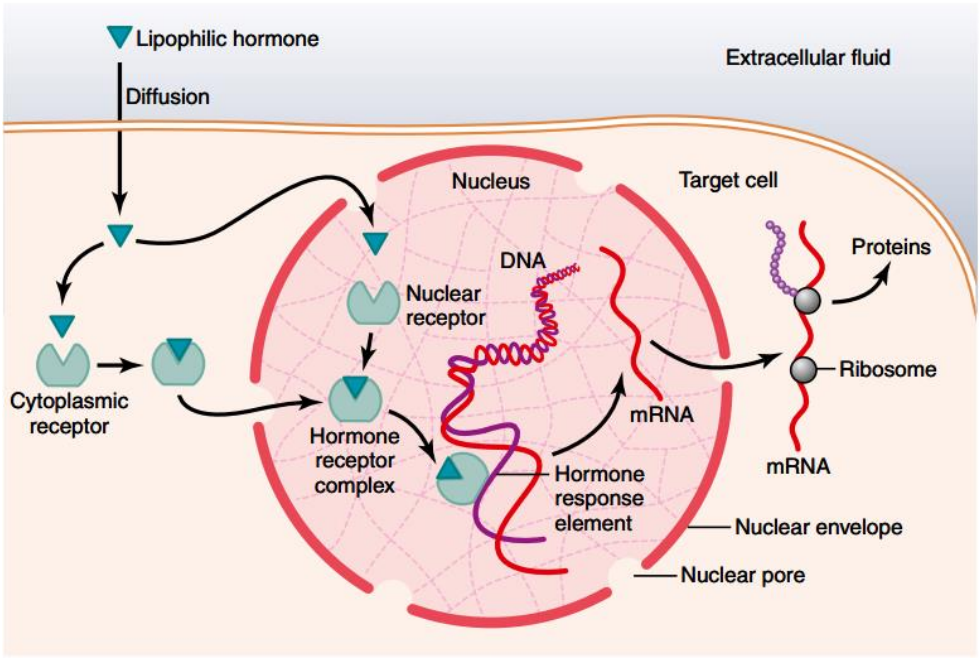
1. The α-subunit binds the enzyme, **phosphoplipase C**
2. Phosphoplipase C breaks down membrane phospholipids (**phosphatidylinositol biphosphate**) to **DAG** and **IP3**.
3. DAG activates **protein kinase C** which in turn, **phosphorylates** other proteins altering their activity
4. IP3 causes **efflux** of Ca^{2+} from the **smooth endoplasmic reticulum** to the cytoplasm.

Angiotensin II (vascular smooth muscle)
Catecholamines (α receptors)
Gonadotropin-releasing hormone (GnRH)
Growth hormone–releasing hormone (GHRH)
Oxytocin
Thyrotropin releasing hormone (TRH)
Vasopressin (V1 receptor, vascular smooth muscle)

Hormones whose effects are mediated by Ca^{2+}

3) Intracellular receptors:

- **Steroid** hormones and **thyroid** hormones can cross the cell membrane.
- These bind **intracellular** receptors rather than membrane receptors.
- Intracellular receptors are either **cytoplasmic** or **nuclear**.
- Binding of the hormone to the receptor causes binding of the receptor to a specific region of the **DNA** affecting its **transcription**.
- Sometimes, **estrogens** and **progesterone** (steroids) effects have to be **rapid**. In this case, they bind cell membrane receptors rather than intracellular receptors, to act **immediately**



Desensitization:

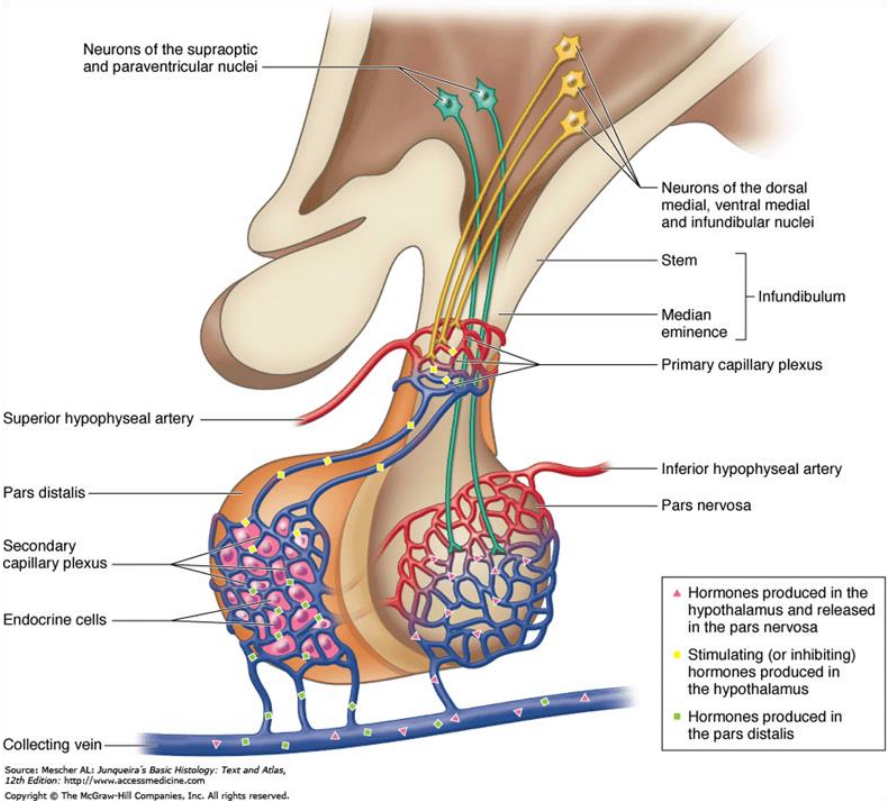
Chronic exposure of the cell to a specific hormone decreases the **number** and **affinity** of the receptors (**down-regulation or desensitization**) . In obese people who have **type 2 diabetes mellitus** (DM), insulin is secreted in normal or **high** amounts but still cells **don't** respond to insulin. The treatment of type 2 DM, especially effective in **early stages**, is **exercising** and **dieting**. Walking is the **easiest** and **cheapest** method to reduce body's fat and weight. This causes the **number** of receptors on the cells and cells' **affinity** to insulin to **increases** (**up-regulation**).

Normal individuals need to walk for **30** minutes **3** times a week to stay **healthy**.

Patients with DM need to walk for **1** hour (6 KM) daily to increase **sensitivity** to **insulin**.

Pituitary Gland (hypophysis)

- **2** portions; **anterior** and **posterior**.
- Lies at the **sella turcica** at the base of the brain.
- **1** cm in diameter.
- **0.5 to 1** gram in weight.
- The anterior pituitary (**adenohypophysis**) is controlled **indirectly** by the hypothalamus.
    - Neurons in the hypothalamus secrete **neurohormones** directly into the **s** of the portal vessels to eventually stimulate (or inhibit) secretions of the anterior pituitary hormones.
- The posterior pituitary (**neurohypophysis**) is controlled directly by the hypothalamus.
    - Cell bodies of special neurons in the hypothalamus synthesize neurohormones which travel along the axons to be stored in posterior pituitary storage cells and released once needed.



Posterior pituitary hormones

- **Oxytocin:**
  - Synthesized by special neurons' cell bodies located in the **paraventricular** nucleus of the hypothalamus.
  - This travels along their axons to be stored in the posterior pituitary **storage** cells and secreted when needed.
  - Its effects on **mammary** glands and **myometrium** were discussed earlier as examples of the positive feedback mechanism.

- **Antidiuretic hormone (ADH):**
  - Synthesized by special neurons' cell bodies located in the **supraoptic** nucleus of the hypothalamus.
  - Secreted as a response to several stimuli, with the 2 most important being 1**) increased ECF osmolarity** 2) **decreased ECF volume**.
  - Mainly, it affects renal **tubules** increasing their permeability to **water** which in turn, increases its **reabsorption**.
  - ADH is also called "**vasopressin**" due to its effect on blood vessels
  - ADH increases blood pressure by 1) **increasing plasma volume**. 2) **constricting blood vessels**.
  - ADH also affects **salivary** and **sweat** to increase their **retention** of water.
- In humans, only **arginine** vasopressin (ADH) is secreted. In some other species, only **lysine** vasopressin is secreted. In others, **both** are secreted.

- Small amounts of oxytocin are also released from the supraoptic nucleus. Small amounts of ADH are also released from the paraventricular nucleus. This is because of the similarity in their structures. Yet, the similarity in their functions is very little.
- In humans, only **arginine** vasopressin (ADH) is secreted. In some other species, only **lysine** vasopressin is secreted. In others, **both** are secreted.

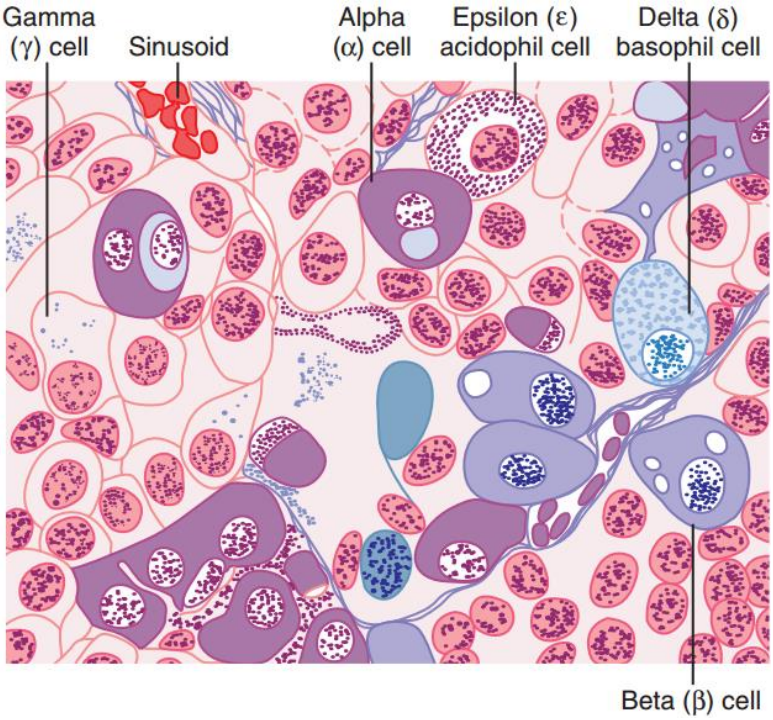
Anterior pituitary

A histological section of the anterior pituitary shows at least 5 different cell types from α to ε. Each cell type secretes different hormones.

Cell type(percentage)	Hormones secreted	Hormones function
Somatotropes (40)	Human growth hormone (**hGH**)	promotes growth of the body
Corticotropes (20)	Adrenocorticotropin hormone (corticotropin , **ACTH**)	controls the secretion of the adrenocortical hormones
Thyrotropes (5)	Thyroid-stimulating hormone (Thyrotropin, **TSH**)	controls the secretion rate of thyroid hormones
Gonadotropes (5)	Gonadotropic hormones, Luteinizing hormone (**LH**) and Folliclestimulating hormone (**FSH**)	control growth of the ovaries and testes and their hormonal activity
Lactotropes (5)	prolactin (**PRL**)	promotes mammary gland development and milk production

Notes

- **Somatotropes** in some cases also secrete **prolactin**, because of the similarity in their structure.



Hypothalamus and Anterior Pituitary

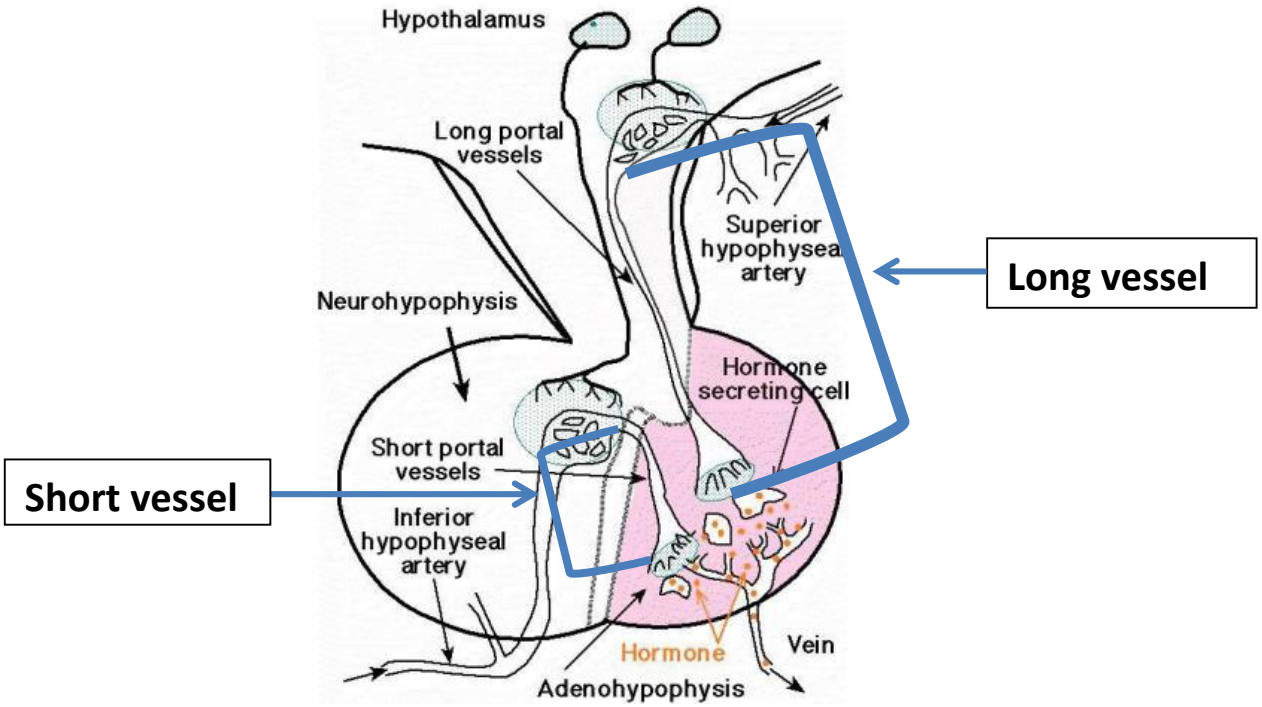
Mechanism of Control

1) Nerve fibers of special neurons in the hypothalamus extend to the **median eminence** into the pituitary stalk.
2) These neurons release hypothalamic inhibitory hormones (**PIH**) and hypothalamic releasing hormones (**others**).
3) These are secreted by nerve fibers to the hypothalamic-hypophysial portal vessels
4) Blood reaches the sinuses in the anterior pituitary.
5) These releasing and inhibitory hormones act on the glandular cells to control their secretions.

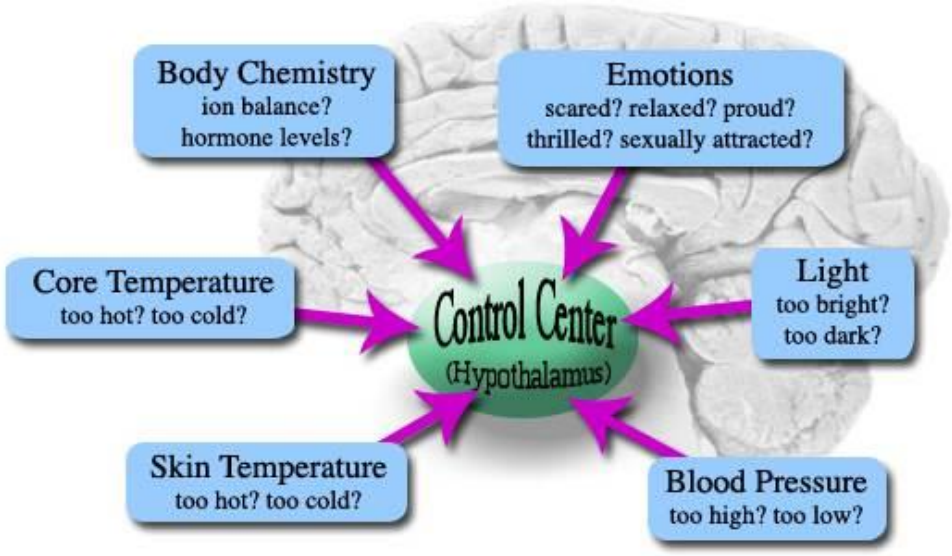
- Hormones released from the hypothalamus reach the anterior pituitary by **2** roots:

1. Neurons release their hormones in **the median eminence** capillary bed and then travel by **long** portal vessels to the adenohypophysis.This long pathway is used when we need **slow** action.

2. Neurons release their hormones in the **posterior pituitary** and travel to the anterior pituitary by **short** portal blood vessels.This short pathway is used when we need **fast** action.



- The hypothalamus is a collecting center for information concerning the internal well-being of the body
- The hypothalamus receives signals from **many** sources in the nervous system.
- This information is used to control **secretions** of the **pituitary** gland.



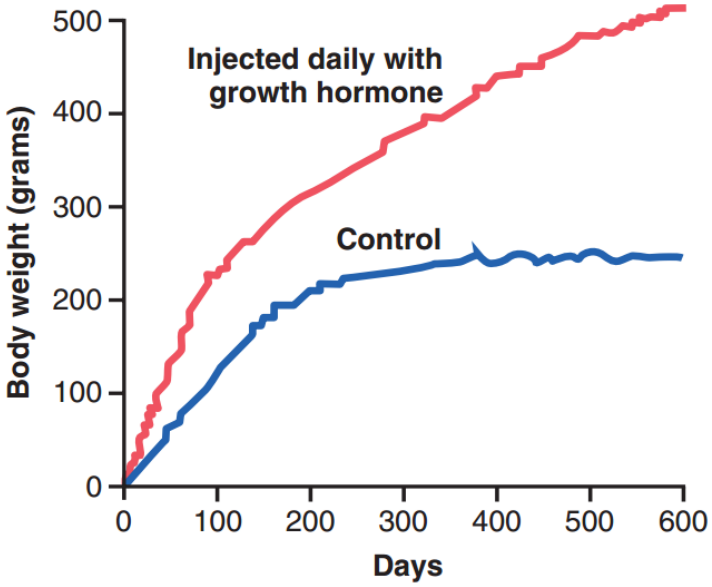
Hypothalamus Hormones

- All hypothalamus hormones stimulate anterior pituitary secretions. Only **PIH** (dopamine) has an inhibitory effect**.**
- **TRH** mainly stimulates the secretion of **TSH**. It also stimulates the secretion of **prolactin**.

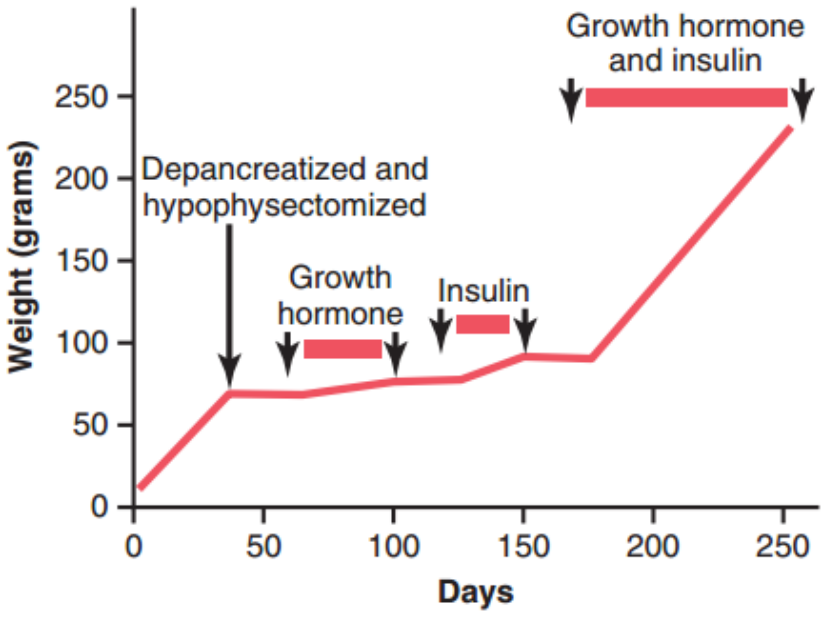
Hormone	Structure	Primary Action on Anterior Pituitary
Thyrotropin-releasing hormone (TRH)	Peptide of 3 amino acids	Stimulates secretion of TSH by thyrotropes
Gonadotropin-releasing hormone (GnRH)	Single chain of 10 amino acids	Stimulates secretion of FSH and LH by gonadotropes
Corticotropin-releasing hormone (CRH)	Single chain of 41 amino acids	Stimulates secretion of ACTH by corticotropes
Growth hormone–releasing hormone (GHRH)	Single chain of 44 amino acids	Stimulates secretion of growth hormone by somatotropes
Growth hormone inhibitory hormone (somatostatin)	Single chain of 14 amino acids	Inhibits secretion of growth hormone by somatotropes
Prolactin-inhibiting hormone (PIH)	Dopamine (a catecholamine)	Inhibits synthesis and secretion of prolactin by lactotropes

Growth Hormone
(hGH, Somatotropic hormone, Somatotropin)

- Exerts its effects directly on **most** tissues of the body, **not** only glands.
- It promotes increased **sizes** of the cells and increased **mitosis**.



- Normal growth also requires other hormones; **insulin**, **thyroid** hormones, glucocorticoids (**cortisol**), **estrogens**, **androgens**, **somatomedins** (Insulin-like growth factors).



Note that

GH alone only very **slightly** stimulated growth.

Insulin alone also very **slightly** stimulated growth, but still **more** than GH.

Together, they **significantly** stimulated growth.

This is an example of **synergism**

- **Growth hormone and insulin like growth factor 1** are the major stimulants of growth.
- GH has **direct** effects and **indirect** effects on tissues.

Direct effects

Metabolic effects:

- Increased rate of **protein** synthesis and deposition
- Increased rates of mobilization and utilization of **fatty acids**
- Decreased rate of **glucose** utilization.

Proteins

- enhances protein synthesis within minutes:
  - Like insulin, it increases the **amino acid uptake** by cells.
  - **Enhances mRNA** translation increasing the amount of proteins in cells.
- Slow effect to increase DNA **transcription**.
- By increasing fat utilization, it acts as a protein **sparer** decreasing catabolism of proteins.

Fats

- Increased release of fatty acids from adipocytes (**lipolysis**).
- Fat is used for energy in preference to use of carbohydrates and proteins.
- If lipolysis greatly increased:
  1) High levels of fatty acids in blood
  2) These enter cells
  3) And are converted to acetyl-CoA
  4) Some of the excess acetyl-CoA is converted to ketone bodies such as **acetoacetic** acid.
  5) This increases blood acidity causing **acidosis**.
- This is called the **ketogenic** effect of GH.

Carbohydrates

- Decreases glucose uptake in tissues
- Increases glucose production by the liver (**gluconeogenesis**)
- These effects cause the blood glucose concentration to raise which in turn stimulates the secretion of **insulin**.
- GH also **directly** stimulates beta cells of the pancreas to secrete insulin.

- This excess insulin **down-regulates** its receptors causing insulin resistance and eventually **type 2 DM**
- This is called the **diabetogenic** effect of GH.

Bones

- Increases growth of the skeletal frame; the **most** obvious effect of GH.
- Increases deposition of protein by the **chondrocytic** and **osteogenic** cells.
- Increases rate of **reproduction** of these cells.
- Converting chondrocytes into **osteogenic** cells, thus causing deposition of **new** bone

Indirect effects

- GH causes mainly the liver to form small proteins called **somatomedins** that have the potent effect of increasing all aspects of **bone** growth.
- Many of the somatomedin effects on growth are similar to the effects of insulin on growth.
- For this reason, the somatomedins are also called insulin-like growth factors (IGFs).
- Somatomedins are **polypeptides** and differ from each other in the **number** of amino acids and the **potency**.
- The most potent is somatomedin C (insulin-like growth factor-1, or IGF-I).

Food intake and GH secretion

Proteins rich meal: insulin and GH are secreted because **both** stimulate amino acid uptake by cells (synergistic effect)

Stimulate Growth Hormone Secretion	Inhibit Growth Hormone Secretion
Decreased blood glucose	Increased blood glucose
Decreased blood free fatty acids	Increased blood free fatty acids
Increased blood amino acids (arginine)	Aging
Starvation or fasting, protein deficiency	Obesity
Trauma, stress, excitement	Growth hormone inhibitory hormone (somatostatin)
Exercise	Growth hormone (exogenous)
Testosterone, estrogen	Somatomedins (insulin-like growth factors)
Deep sleep (stages II and IV)	
Growth hormone–releasing hormone	
Ghrelin	

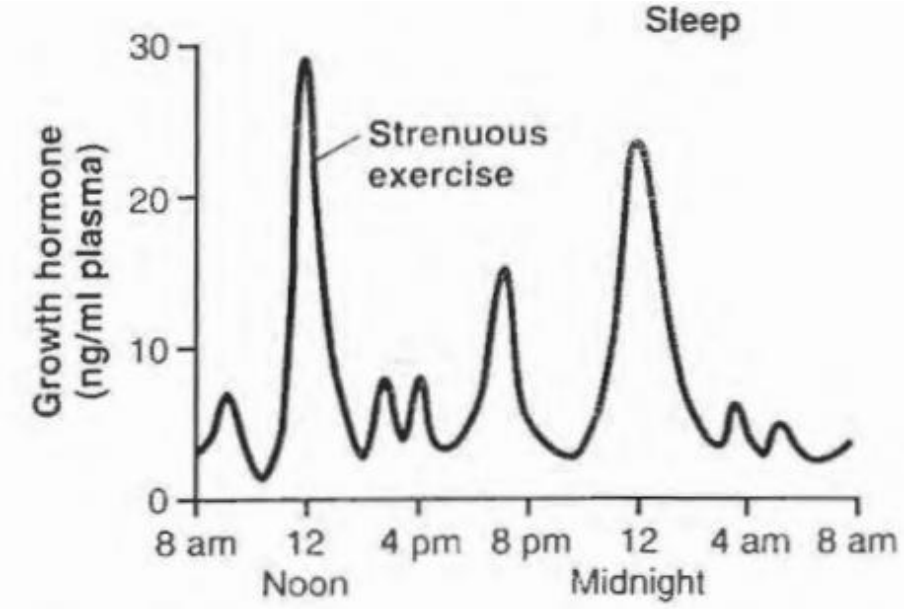
Crabohydates rich meal: only **insulin** is secreted because it stimulates glucose uptake.

Fasting: only **GH** is secreted because it inhibits glucose uptake.

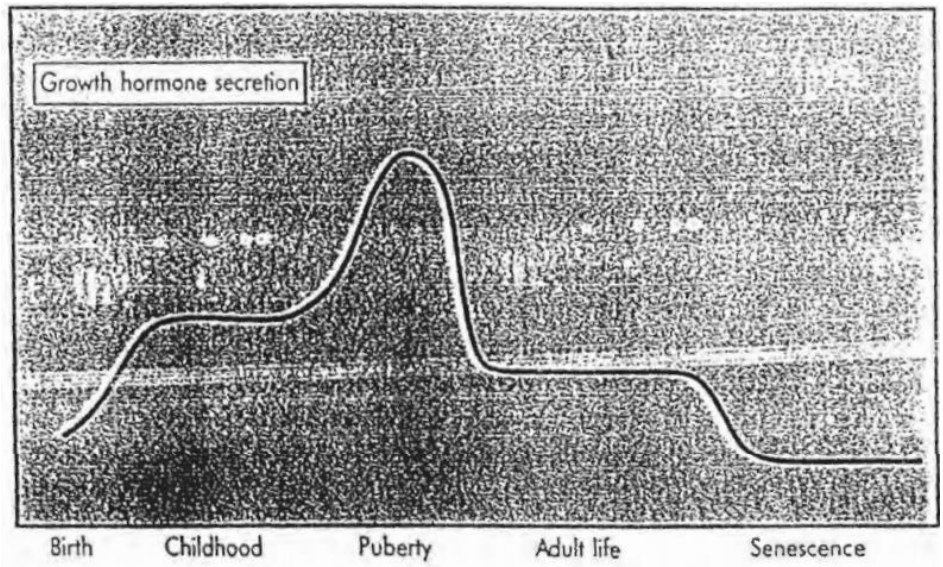
Ghrelin is a hormone secreted by the stomach and small intestines to **increase** the appetite.

Somatomedins inhibits additional GH

secretion.



This is the **diurnal** rhythm (over 24 hours) of GH



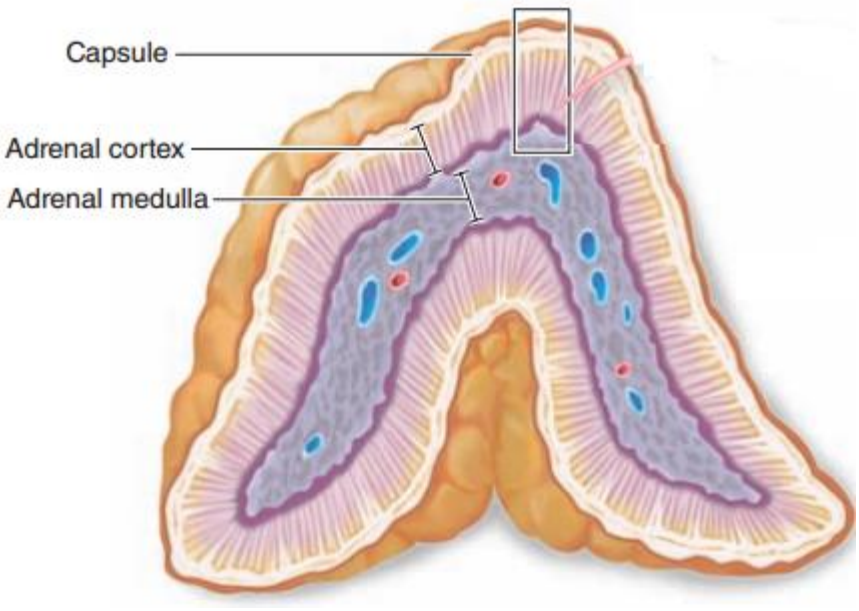
This is the **developmental** rhythm of GH (throughout different stages of life)

The difference **isn't** significant (less than 10%) between children and adults

- Many GI hormones affect food intake and appetite.
- Leptin is produced by fat cells to inhibit appetite.
- Eating too much dilates the stomach causing obesity.

Adrenocorticotropic Hormone (ACTH)

- ACTH is a **peptide** hormone secreted from the **anterior** pituitary.
- Its secretion in the fetus begins very **early** in uterine life, before the development of the adrenal cortices.
- It stimulates the secretions of the adrenal **cortices**.
- ACTH (**corticotropin**) secretion is stimulated by
  - **CRH** (corticotropin releasing hormone) from the hypothalamus.
  - **ADH** (antidiuretic hormone) from the posterior pituitary.
- ACTH responds to many types of stresses.



- Each adrenal gland is composed of 2 parts; the adrenal medulla and adrenal cortex.

- They are very different in their histology, function, and embryological origin.

- Each weighs **3-5** grams.

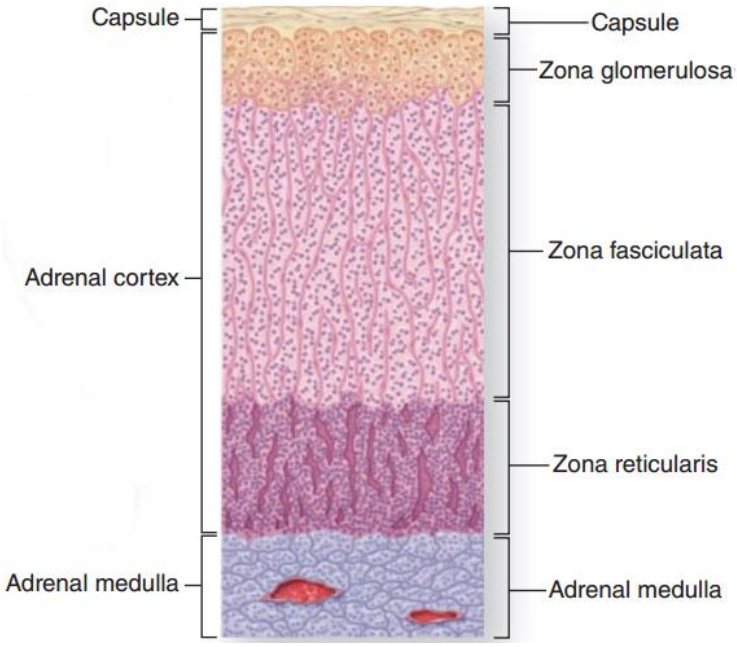
This section shows the capsule of the gland, adrenal cortex and the adrenal medulla.

3 zones of the adrenal cortex:

Zona glomerulosa (12%)

Zona fasciculata (65%)

Zona reticularis (23%)



Zona glomerulosa

- Just underneath the capsule.
- Cells of this zone secrete steroid hormones called **mineralocorticoids**.
- The most potent is **aldosterone**.

Zona fasciulata

- Cells of this zone secrete steroid hormones called **glucocorticoids** in addition to small amounts of **androgens** and **estrogens**.
- The most potent of these is **cortisol**.

Zona reticularis

- Cells of this zone secrete **androgens** and small amounts of cortisol.
- They don't differentiate until age 8.
- Cells of the zona glomerulosa **migrate** down to reach the zona reticularis. Their shape and function changes along the way.

	Glucocorticoid activity	**Mineralocorticoid activity**	**Plasma concentration**	**Secretion rate(mg/day)**
Cortisol	**1**	**1**	**12**	**15**
Aldosterone	**0.3**	**3000**	**0.006**	**0.15**

Note that cortisol is an **active** mineralocorticoid beside its glucocorticoid activity. Aldosterone is a relatively **inactive** glucocorticoid; it **only** has an important mineralocorticoid activity.

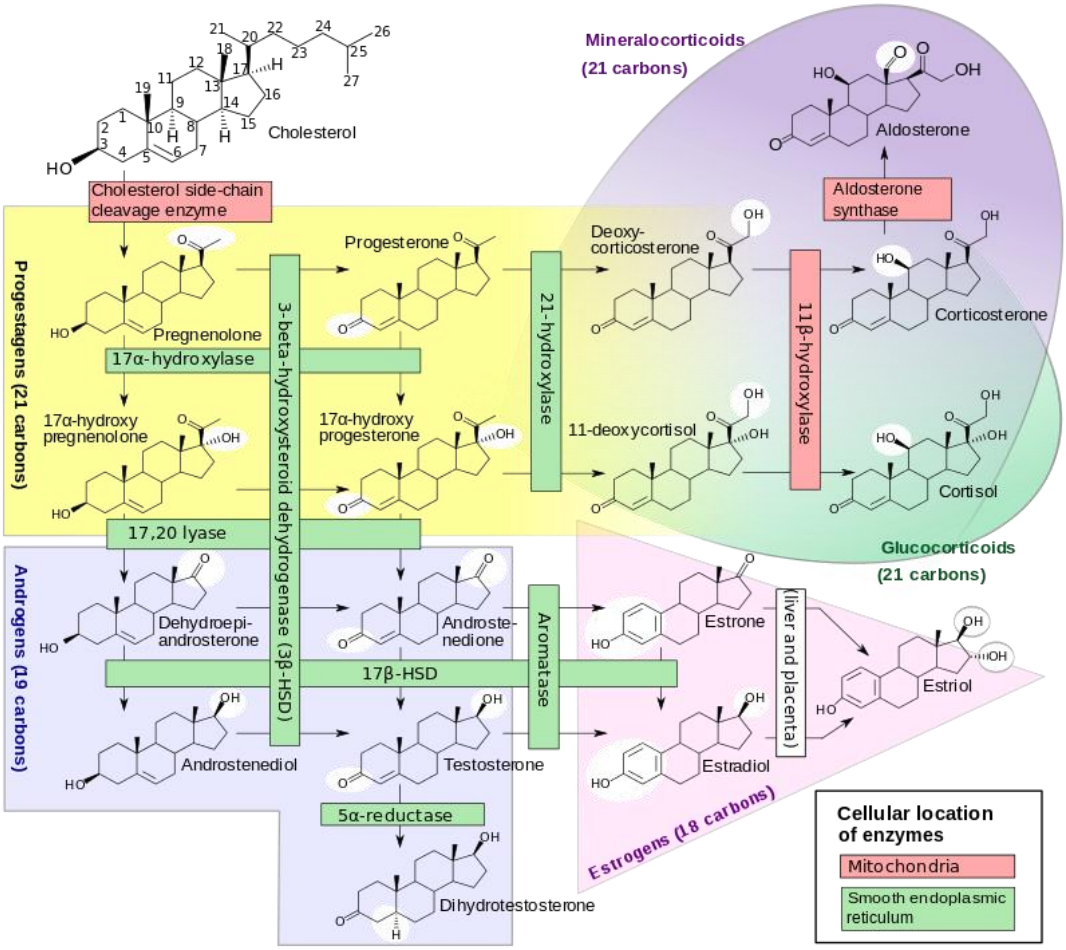
From the table, we can obtain each hormone's glucocorticoid and mineralocorticoid activity **contribution** in the body.

	Glucocorticoid contribution (glucocorticoid activity X plasma concentration)	**Mineralocorticoid contribution (mineralocorticoid activity X plasma concentration)**
Cortisol	**12**	**12**
Aldosterone	**0.018**	**18**

Note that aldosterone contribution to the glucocorticoid activity is **negligible**.

Important: as seen, cortisol contribution to the mineralocorticoid activity is **significant**. This is **not true** in our bodies because the epithelial cells of the kidney which contain aldosterone receptor, express an **enzyme** which **immediately inactivates** cortisol upon entry into the cell preventing it from binding the receptor. A **deficiency** of this enzyme allows cortisol to contribute **significantly** to the mineralocorticoid activity as if **alodosterone** is secreted in very high amounts.

- Most of the cortex secretion is **cortisol** (mainly from zona fasciculata)
- **ACTH** targets this zone; it stimulates these cells to release cortisol.
- Cortisol, like other cortex hormones, is a steroid synthesized from cholesterol.



A change in even a single enzyme that catalyzes a single step causes vastly different types and relative **proportions** of hormones to be formed.

For example, deficiency in the enzyme that catalyzes the last step of the synthesis of cortisol:

1. Increases the levels of **deoxycortisol**, **11-deoxycorticosterone** and **androgens** (dehydroepiandrosterone and androstenedione**)**
2. Decreases the levels of **aldosterone** and **corticosterone**.

In many mammals, including **rats**, **corticosterone** is the main glucocorticoid with cortisol being absent.

Adrenal cortex cells don't store hormones. Once stimulated, they synthesize the hormones and **immediately** secrete them.

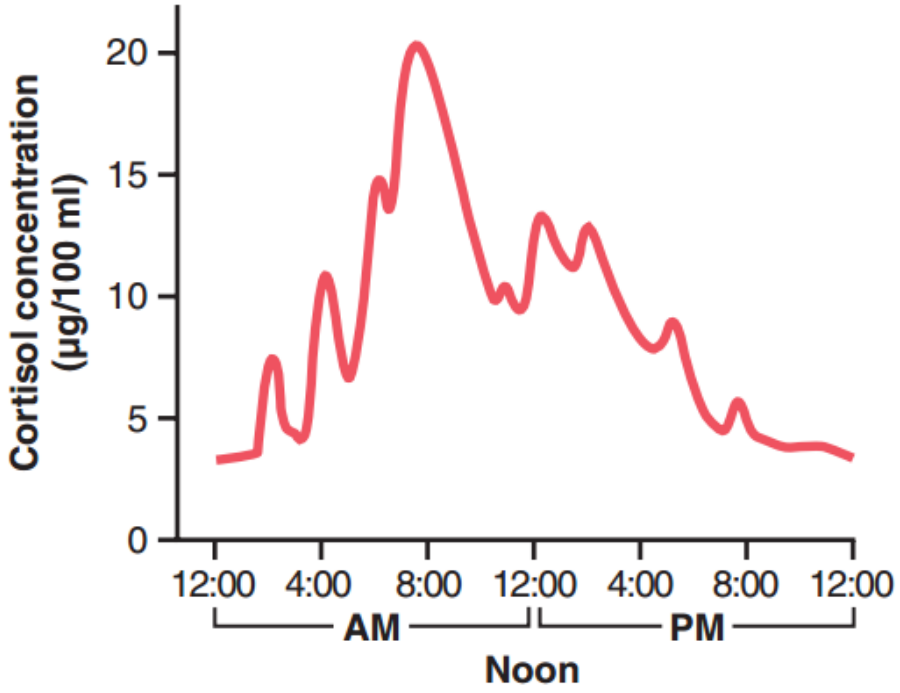
Cortisol

Being **lipid** soluble, it's **bound** to plasma proteins in the blood:

- **90%** of cortisol is bound to cortisol binding globulin (**transcortin**).
- **6%** of cortisol is bound to albumin.
- **4%** of cortisol is free to diffuse into cells.
- An **equilibrium** is maintained between free and bound cortisol.
- Only the **free** cortisol is the functional cortisol.
- Half-life: **60** to **90** min.

Cortisol is **essential** to life, especially while **fasting**, because glucose level decreases and **glucagon** has to act to return it to its normal level.

Diurnal rhythm of cortisol



Effects of cortisol

1) Alter metabolic activities

Carbohydates

1. **Stimulates gluconeogenesis:**
   It doesn't stimulate gluconeogenesis itself; it just has a **permissive** action to glucagon. (Without cortisol, glucagon fails to stimulate gluconeogenesis).
2. **Decreases glucose utilization by cells**

Proteins

1. **Decreases amino acids uptake by cells.**
   These amino acids diffuse to the liver which in turn uses them as **substrates** for gluconeogenesis and synthesizes **plasma proteins**.
2. **Increase mobilization of proteins from nonhepatic tissues**

Fats

1. **Promotes mobilization of fatty acids by adipocytes**
   This causes the cells to utilize energy from Fatty acids rather than glucose in times of starvation or other stresses. This in turn **conserves** glycogen stores.

2) **Suppresses immunity and inflammation (anti-inflammatory)**
3) **Responds to stresses**
4) **Modulates the functions of the nervous system.**

Cortisol is also essential in fetal life:

1) **Production of surfactants from type 2 cells of the alveoli.**
   Surfactants lack causes respiratory distress syndrome.
   Injection of minute quantities of cortisol in new born babies who lack surfactants stimulates their production immediately and they start to breathe properly within minutes.
2) **Development of hypothalamic function and of the thyroid pituitary axis**
3) **Causes the sequential changes of the placental structure and the composition of the amniotic and allantoic fluids.**
4) **Very important in the initiation of parturition.**

5) **Formation of the hepatic enzymes including those involved in gluconeogenesis.**
6) **Induction of thymic involution**

- Cortisol and its derivatives are used as effective medications in most diseases especially those with no known reasons and medications “The magic drug”. This is because they enters all cells and affect those which have its receptor**.**

Some glucocorticoids:

- Cortisol: Natural , provides 95% of the total glucocorticoid activity.
- Corticosterone: Natural, provides 4% of the total glucocorticoid activity.
- Cortisone : Synthetic .
- Prednisone : Synthetic. The **most** commonly used.
- Methylprednisone : Synthetic .
- Dexamethasone: Synthetic . The most potent (**30** times as cortisol).

Aldosterone

These hormones control **minerals** metabolism (Na^+, K^+), **water** reabsorption, blood **volume** and consequently, blood **pressure**.

Aldosterone is **essential** to life; its absence causes death within days.

Excess aldosterone greatly increases blood pressure (hypertension) which eventually causes kidney failure.

Being lipid soluble, it’s bound to plasma proteins in the blood:

- **20%** of cortisol is bound to corticosteroid-binding globulin (transcortin).
- **40%** of cortisol is bound to albumin.
- **40%** of cortisol is free to diffuse into cells. (high compared to others)
- An **equilibrium** is maintained between free and bound cortisol.
- Only the **free** aldosterone is the functional aldosterone.
- Half-life: relatively **short**. **20** min

The main stimulants of its secretion are angiotensin 2, 3 and K^+ concentrations. ACTH only slightly stimulates its secretion.

Additional Info: Small amount of ACTH is enough to **permit** the adrenal glands to secrete whatever amount of aldosterone is required, but total absence of ACTH can significantly reduce aldosterone secretion.

Therefore, ACTH plays **permissive** role in regulation aldosterone secretion

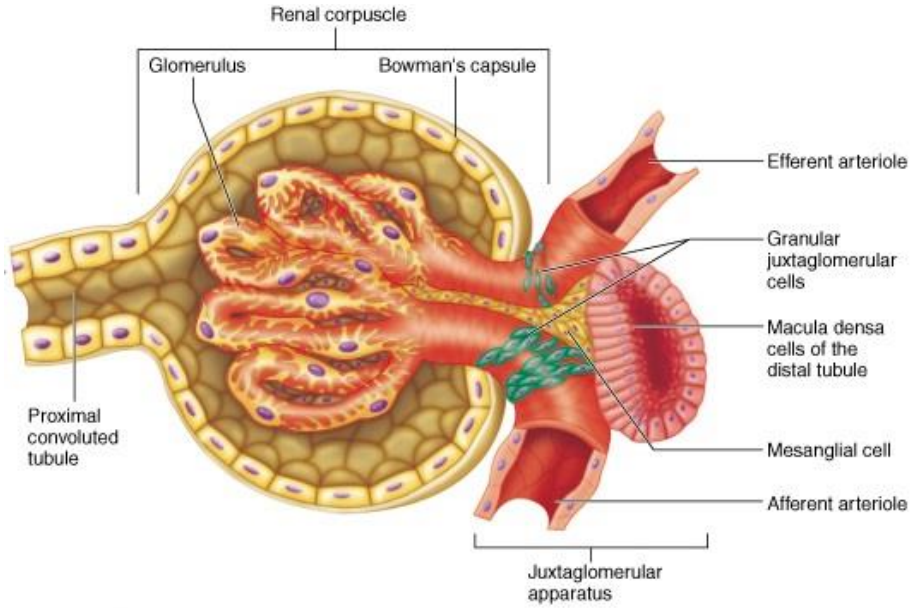
Renin-Angiotensin 2 system

1) Decreased blood pressure, plasma volume, Na^+ concentration stimulates
2) Juxtaglomerular apparatus of the kidney produces renin enzyme. Renin cleaves **angiotensinogen** (a protein secreted by the liver) to form **angiotensin 1** which is further cleaved by **angiotensin-converting enzyme (ACE)** to form **angiotensin 2**.

   ACE inhibitors drugs are **commonly** used to reduce blood pressure because they are very **safe** drugs with no side effects

3) Angiotensin 2 has:

- **Indirect** effect in stimulating **aldosterone** secretion.
- **Direct** effect in increasing **Na^+** reabsorption.
  Blood enters **Bowman's** capsule in the afferent arteriole and leaves through the efferent arteriole.
- Angiotensin 2 constricts the efferent arteriole.
- The fluid in the peritubular capillaries is reduced while protein concentration remains the same
- This indirectly increases the colloidal osmotic pressure and water is reabsorbed followed by Na^+.

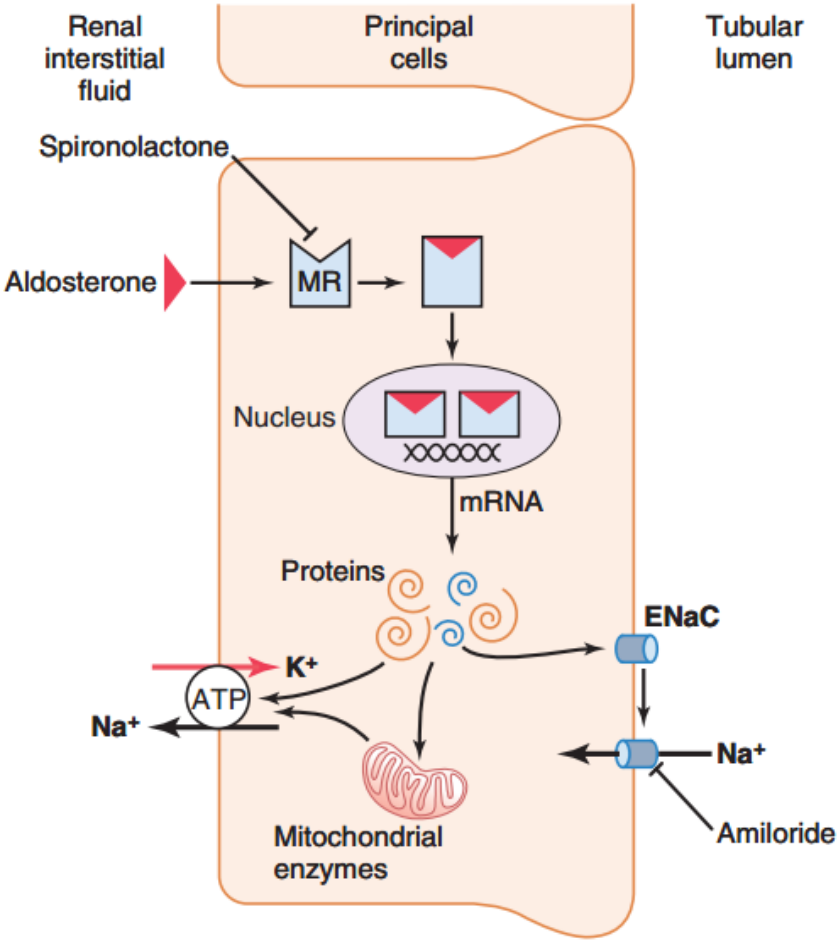


Angiotensin 3 and 4 do the same effects as angiotensin 2 but with **lower** potencies.

Aldosterone also stimulates retention of water from **intestines**, **salivary** and **sweat** glands.

Other mineralocorticoids include: deoxycorticosterone, corticosterone, flurocortisone, cortisol and cortisone. Cortisol is used as a medication.

Mechanism of action of aldosterone



1) Aldosterone enters the cell and binds a specific **cytoplasmic** mineralocorticoid receptor (**MR**)

2) This complex enters the nucleus and induces **transcription** of DNA.

3) Proteins are produced to increase Na^+ reabsorption:
1. Na^+ / K^+ ATPase , at the basolateral membrane of the renal tubular cell.

2. Epithelial Na^+ channel (ENaC) inserted into the luminal membrane.

Note: The **filtrate** is in the tubular **lumen**. Along its way to form urine, **reabsorption** of materials occurs at the luminal (**apical**) membrane of the epithelial cells. Reabsorbed materials are then transported from the **basolateral** membrane of the cells to the interstitial fluid and eventually the **blood**. Na^+ diffuses from the tubules to the epithelial cells through **ENaC** and actively transported from the cell to the interstitial fluid in exchange with **K^+**. Aldosterone increases transcription of both **ENaC** protein and **Na^+/K^+ ATPase** enzyme.

Note: increased K^+ concentration in the interstitial fluid itself **stimulates** the secretion of aldosterone.

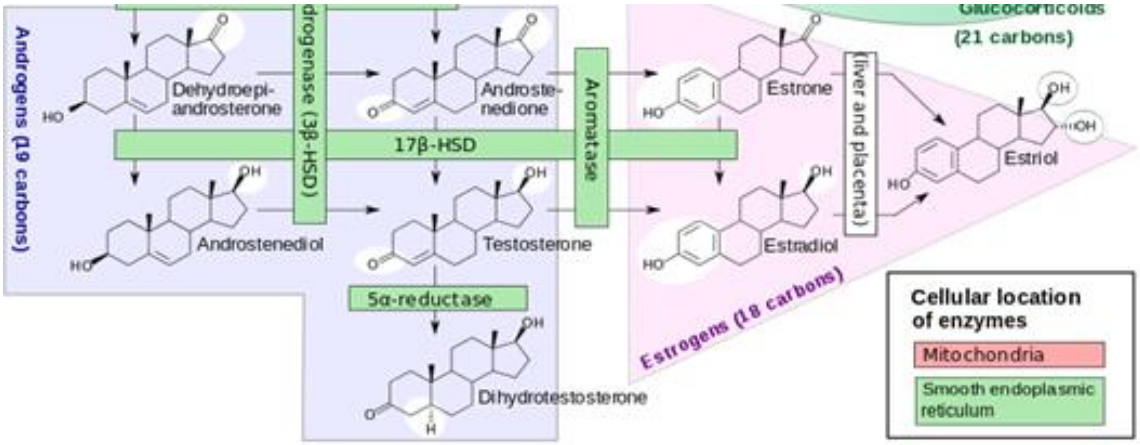
Spironolactone blocks MR receptor, amiloride blocks ENaC. Both drugs reduce blood pressure

Androgens and Estrogens

The main androgen produced is **d**e**h**ydro**e**pi**a**ndrosterone (**DHEA**) which is converted into **androstenedione**. Both are **weak** androgens.

They are converted into **testosterone**. It is the **most potent** androgen.

Androstenedione is converted into **estrone** and testosterone is converted into **estradiol**. Both are estrogens



Function of androgens

Presence of pubic and axillary hair and libido (sexual desire)

They are **not** important in **males** in any stage of life. However, their **over**-**secretion** in childhood causes rapid development of male sexual organs (**adrenogenital syndrome**)

They are **important** in **females** in all stages of life, especially after **menopause,** when the ovaries stop secreting hormones and the adrenal cortex becomes their **only** source.

Thyroid releasing hormone (TRH):

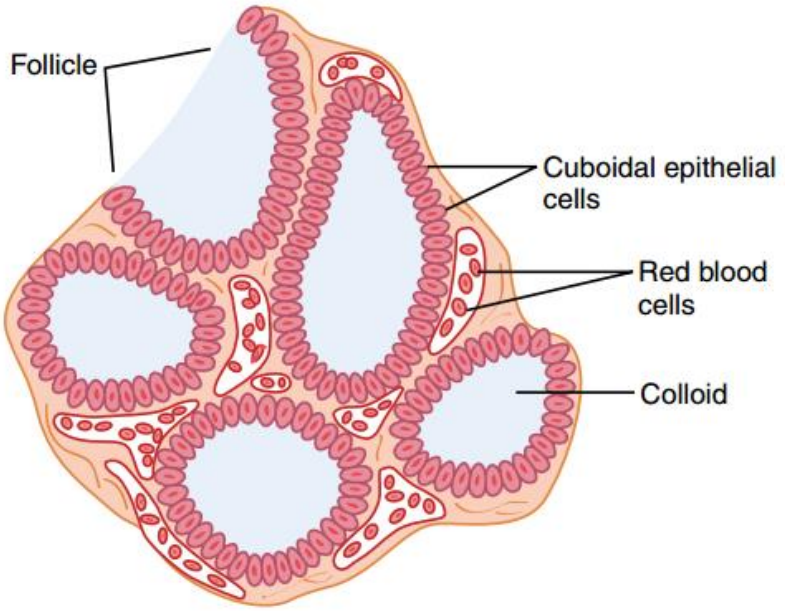
- Very **short** polypeptide; only **3** amino acids.
- Released from **hypothalamic** nerves into the hypophyseal vessels to reach the **anterior** pituitary.
- It binds to **thyrotropes** in the anterior pituitary.
- This Increases Phospholipase C activity and **Ca^{2+}** second messengers.
- This eventually leads to **TSH** release and an increase in its **bioactivity**.
- To a lesser extent, It also binds to lactotropes to stimulate **prolactin** secretion

Thyroid stimulating hormone (TSH):

- **Glycoprotein** hormone
- Composed of 2 subunits; **α and β**.
- **α** is **non-specific** and found in other hormones; FSH, LH and CGH (Chorionic Gonadotropic Hormone). It's **necessary** for the hormone to function.
- **β** is the **specific** and **active** subunit.
- Released from the anterior pituitary.
- **Dopamine** and **somatostatin** directly inhibit its secretion.
- **Cortisol** and **growth hormone** indirectly inhibit its secretion, most probably by stimulating the secretion of **somatostatin**.
- It increases the activity of
    - Adenyl cyclase and **cAMP** second messenger: **Immediate**:
        - **synthesis** of the hormones
        - **Secretion** of the hormones
    - Phospholipase C and **Ca^{2+}** second messenger: **Prolonged**:
        - **Metabolism** of thyroid cells.
        - **Growth** of thyroid glandular tissue.

Thyroid Gland

- Weighs **25-30** grams
- Right and left lobes joined by the **isthmus** which lies in front of the trachea
- Start functioning at the **12^{th}** week of gestation.
- Maternal **TSH** and **TRH** don't pass through the **placenta** to the fetus.
- The cuboidal cells that surround the colloid secrete thyroid hormones:
    - **Triiodothyronine (T_3)**
    - **Tetraiodothyronine (thyroxine, T_4)**

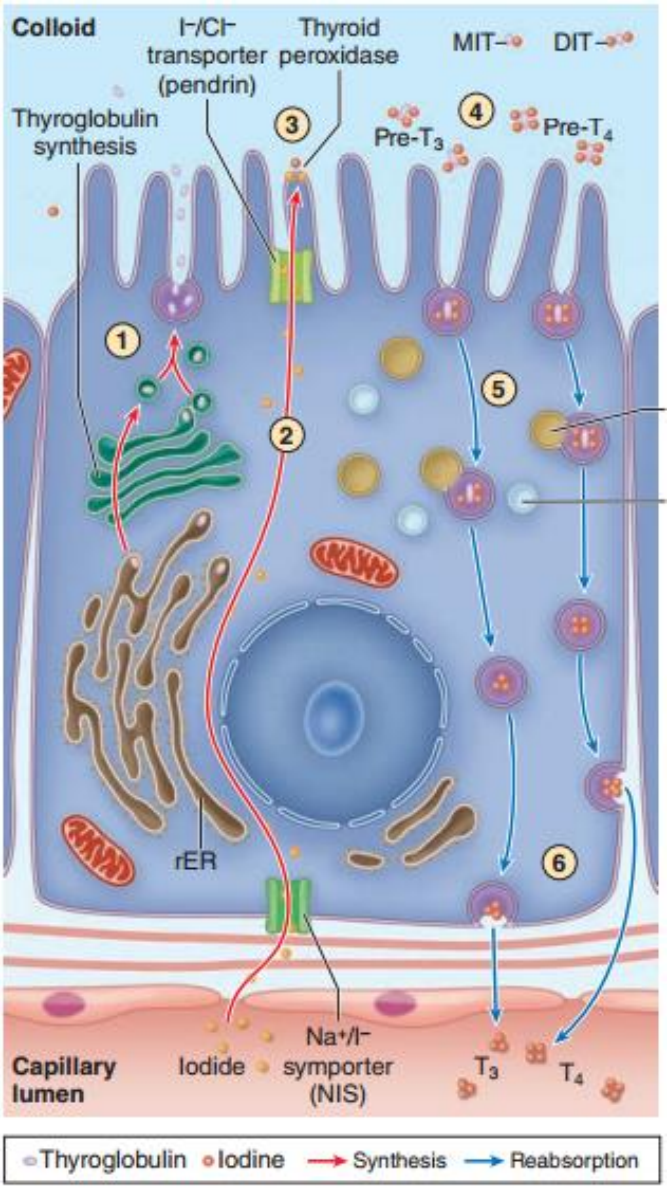


Composed of follicles with abundant blood supply.

The follicle is colloid surrounded by cuboidal epithelial cells

Other cells (C, clear, parafollicular) cells secrete calcitonin.

Synthesis of thyroid hormones



1-Thyrogolbulin (**100 to 120** tyrosyl residues) is synthesized in ER, gylcosylated in golgi and secreted into the follicle by exocytosis at the **apical** membrane of the cuboidal cell.

2- **2Na$^+$** for each **I$^-$** enter the cell leaving the blood at the basal membrane by the action **of Na$^+$/I$^-$ symporter (NIS). (Iodide trapping)**

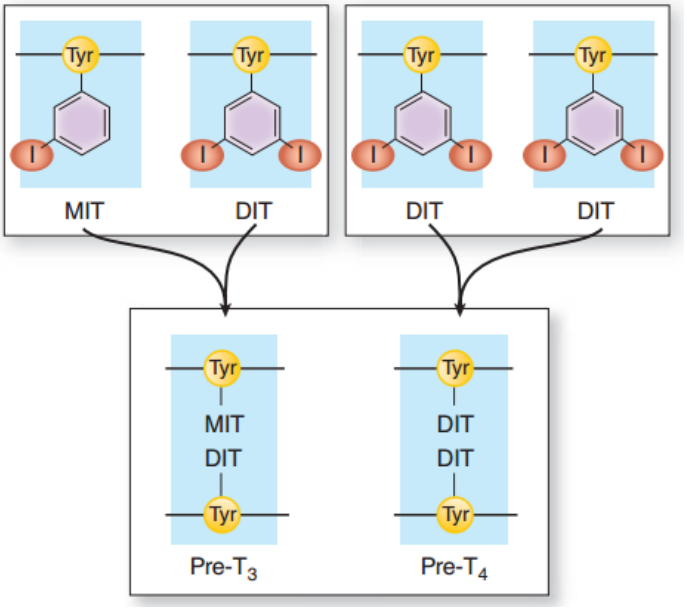
3- **I$^-$/Cl$^-$** transporter (**pendrin**) pumps I$^-$ from the cell into the colloid.

4- Membrane-bound thyroid peroxidase enzyme on the microvilli surface oxidizes iodide to iodine.

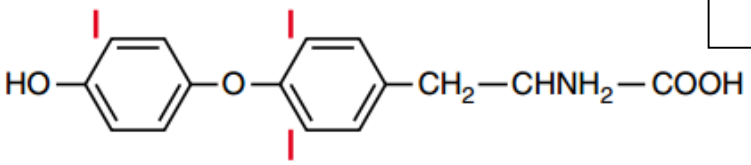
5- In the colloid, 1 or 2 iodine atoms are bound to 70 tyrosyl residues forming either MonoIodoTyrosine (**MIT**) or DiIodoTyrosine (**DIT**).

6- MIT or DIT are **covalently coupled** to form **pre-T$_3$** or **pre-T$_4$** or **pre-RT$_3$** within the protein.

7- The iodinated thyroglobulin enters the cell by pinocytosis and is degraded by lysosomes, releasing **free** active T3 and T4 to the adjacent capillaries in an endocrine manner. (only 4-8% produce final hormones)

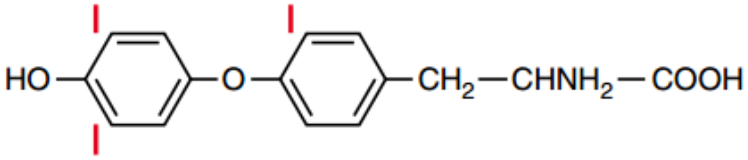


Monoiodotyrosine + Diiodotyrosine →



3,5,3'-Triiodothyronine (T_3)

Diiodotyrosine + Diiodotyrosine →



3,3',5-Triiodothyronine (RT_3)

T4 is a **prohormone**

It produces the other hormones

T2 is **diiodothyronine**.

T4 (**almost inactive**)

T3 (**Most active**)

rT3 (**Inactive**)

T2 (**Inactive**)

	T_4	T_3	rT_3
Daily production (µg)	90	35	35
From thyroid (%)	100	25	5
From T_4 (%)	—	75	95
Extracellular pool (µg)	850	40	40
Plasma concentration			
Total (µg/dl)	8.0	0.12	0.04
Free (ng/dl)	2.0	0.28	0.20
Half-life (days)	7	1	0.8
Metabolic clearance (L/day)	1	26	77
Fractional turnover per day (%)	10	75	90

Most of its secretions is **T4**.

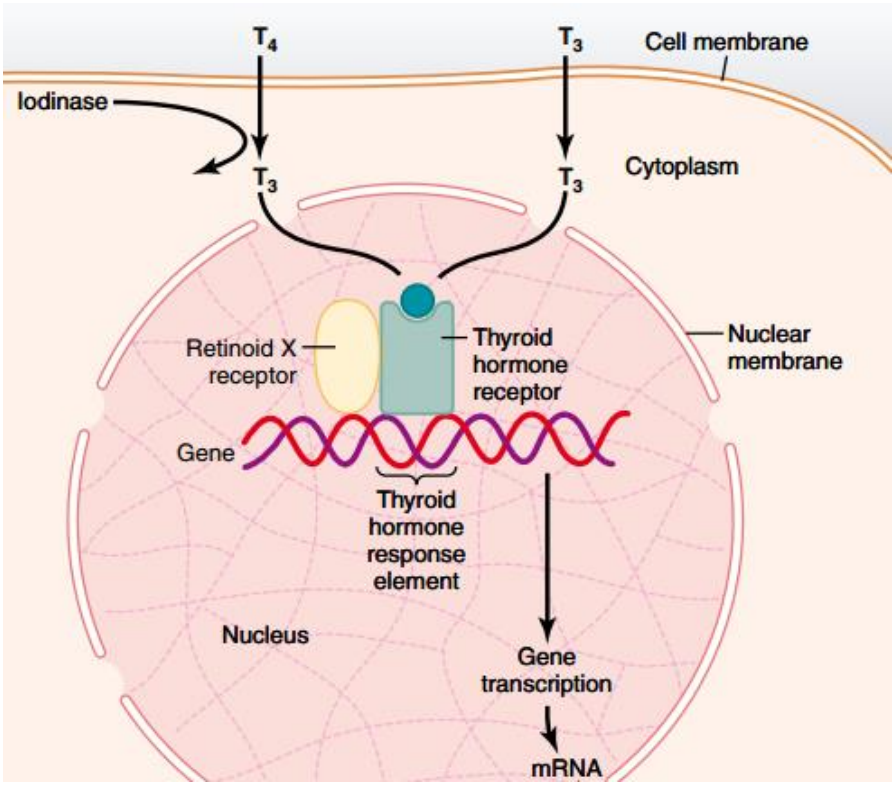
Most of T3 and rT3 is produced from T4

T4 and T3 inhibit their secretion by affecting the hypothalamus, pituitary and thyroid glands.

	T4	T3
Thyroid binding globulin	**75**	**75**
Albumin	**10**	**25**
Thyroxine-binding prealbumin	**15**	**0**
Total	**99.98**	**99.5**

In the blood, Thyroid hormones are **bound** to plasma proteins. This prevents the filtration of the hormones through the glomeruli prolonging their **half-lives**.

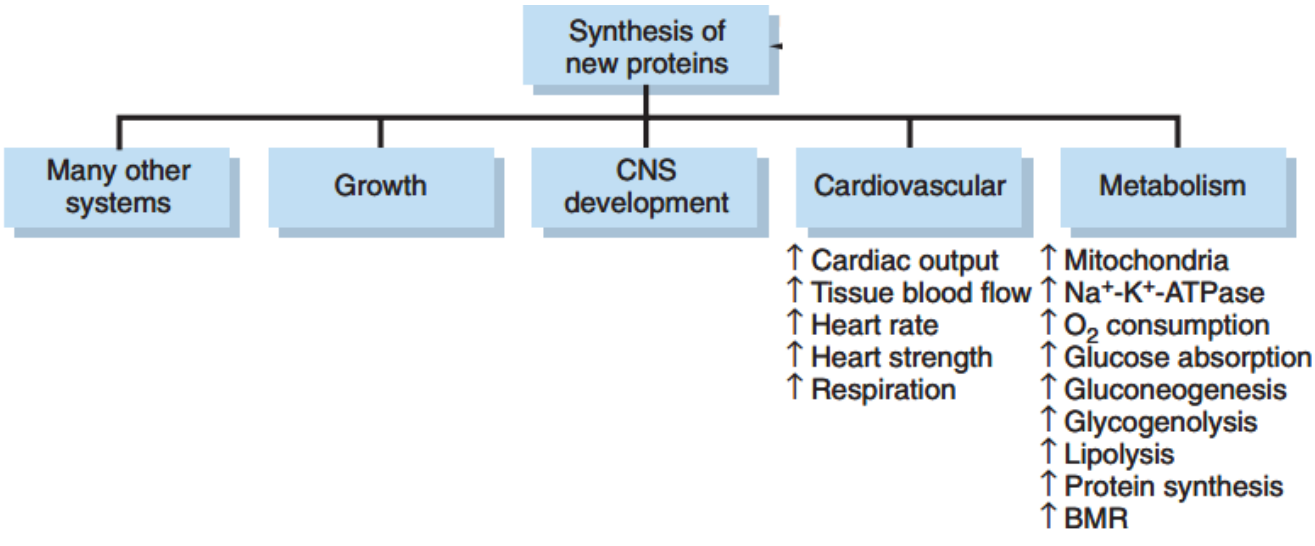
- In the target cell, both (especially T_4) again bind with **intracellular** proteins and are stored to be slowly used.



1) In the target cell, **iodinase** removes one I^- from T_4 to form T_3 which has a much higher affinity for intracellular receptor.

The receptor forms a **heterodimer** with retinoid X receptor (**RXR**) at specific thyroid hormone response elements on the DNA

2) T_3 binds to the receptor to activate it and initiate **transcription** and translation



Stimulate thyroid hormones secretion	Inhibit thyroid hormones secretion
TSH	Iodine deficiency
Thyroid-stimulating immunoglobulins	Deiodinase deficiency
Increased TBG levels (pregnancy)	Excessive Iodine intake (Wolff-Chaikoff effect).
	Perchlorate, thiocyanate (inhibit I^- pump)
	Decreased TBG levels (e.g., Liver disease).
	Propylthiouracil (inhibits peroxidase).

- Thyroid Hormones are **essential** for growth
- An Excess in thyroid hormones **doesn't** result in giantism as with GH.
- Thyroxine has a **permissive** effect to GH in protein synthesis. So, in its absence, amino acids uptake and protein synthesis are not much stimulated.

Hypopituitarism

Panhypopituitarism

- Decreased secretion of **all** the pituitary hormones
- **Posterior** pituitary:
  - **ADH** deficiency:
    decrerased water reabsorption, increased water in urine and polyuria, diabetes insipidus (DI, bale urine rather than the dark urine of DM patients).
  - **Oxytocin** deficiency:
    Uterine contractions and milk ejection are not seriously affected.
- **Anterior** pituitary
  - **FSH/LH** deficiency:
    - **Males**: no testosterone, decreased libido (sexual desire), no sperms (infertility), loss of body hair.
    - **Females**: no progesterone and estrogen, decreased libido, amenorrhea (no menstrual cycles).
  - **TSH** deficiency: atrophy of the thyroid gland, weight gain, lethargy.
  - **ACTH** deficiency: atrophy of the adrenal cortex, weight gain.

- **GH** deficiency: dwarfism, development of all parts of the body in appropriate proportion. Mental abilities are not affected.
- **MSH** deficiency: pallor color.

Severe anterior pituitary deficiency

Similar to the results above but ADH and oxytocin secretion is normal

Moderate anterior pituitary deficiency

- FSH, LH and TSH are **deficient**.
- ACTH & MSH are **partially** deficient.
- GH is **normal**

Mild anterior pituitary deficiency

- FSH and LH are deficient.
- Other hormones are normal

Hyperpituitarism

Oversecretion of the pituitary hormones

Usually because of a tumor.

- **Before adulthood (Giantism or gigantism)**
  - The gland gets larger.
  - Bone and all other organs become very large but in appropriate proportions.
  - Patients are very tall.
  - Hyperglycemia, with 10% develop DM.
  - Without treatment, the tumor which caused hormones' oversecretion eventually destroys pituitary gland cells causing panhypopituitarism
- **After adulthood (acromegaly)**
  - Long bones don't grow in length; patients are not very tall.
  - Bones (especially membranous bones) become thicker. This can cause osteopetrosis.
  - Soft tissues continue to grow with no appropriate proportion.

Hypothyroidism

Cretinism

- Deficiency of thyroid hormones in **childhood**.
- Caused by genetic factors (**congenital** cretinism) or iodine deficiency (**endemic** cretinism).
- These children are **dwarfs** and mentally **retarded**.
  - Note: Children with GH deficiency are dwarfs but mentally **normal**.
- Thyroid hormones from the mother make the neonate look normal with symptoms start after **weeks**.
- Skeletal growth is more inhibited than the soft tissue.
- This results in **disproportionate** rate of growth; the soft tissues enlarge excessively
- Patients are **obese** and **short**.
- Occasionally the tongue becomes so large in relation to the skeletal growth that it obstructs **swallowing** and **breathing**
- **Iodine** or **thyroxine** can be given **any time** after birth to return normal **physical** growth but they must be given within **a few weeks** after birth to return normal **MENTAL** growth.

Simple benign goiter (nontoxic)

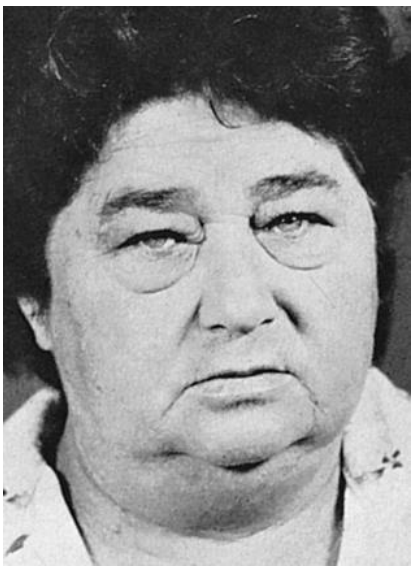
- The term "goiter" means a greatly **enlarged** thyroid gland.
- Two types; **endemic** and **idiopathic**.
- Nontoxic because T_3 and T_4 levels are usually (not always) low (hypothyroidism)

1. **Endemic goiter**
   - Endemic in areas where iodine intake is **not** sufficient.
   - Iodine in **table salt** is sufficient to prevent it.
   - **Mechanism**:
     1) Iodine is deficient.
     2) Thyroid hormones synthesis doesn't occur.
     3) TSH secretion is not inhibited
     4) TSH stimulates secretion of thyroglobulin colloid into the follicle with no feedback inhibition.
     5) The follicles become tremendous in size.
     6) The gland grows larger and larger
2. **Idiopathic goiter**

- Idiopathic (the exact cause is not known).
- Patients do not have iodine deficiency.
- The secretion of the hormones is depressed but sometimes normal.
- **Mechanism:**
  1) Thyroiditis causes slight hypothyroidism.
  2) This leads to increased TSH secretion.
  3) The noninflamed portions of the gland progressively grow.
  4) The gland grows larger and larger

Myxedema

- Bagginess under the eyes
- Swelling of the face.
- Body's functions are slowed down.
- Develops in persons who have **almost total** lack of thyroid hormone function.



Hyperthyroidism

Grave's disease

- Most common.
- Antibodies called thyroid-stimulating immunoglobulins (**TSIs**) form against the TSH receptor in the thyroid gland
- These antibodies bind with the same receptors that bind TSH resulting in the same effects of TSH itself.
- High thyroid hormones suppress TSH secretion to almost **zero**.

Thyroid adenoma

- A tumor that develops in the thyroid tissue and secretes large quantities of thyroid hormone.
- The hormone secretion from tumor cells suppresses TSH secretion.
- Thyroid hormones secretion from the normal part of the gland is suppressed.

- Thyroid hormones secretion from the tumor is not suppressed increasing their levels and causing hyperthyroidism.

Exophthalmos

- **Protrusion** of the eyeballs
- Occurs in **most** patients with hyperthyroidism.
- Sometimes severe that the eyeball protrusion stretches the **optic nerves** enough to damage vision.
- Much more often, the eyes are damaged because the **eyelids** do not close completely when the person **blinks** or is **asleep**. As a result, the epithelial surfaces of the eyes become **dry** and **irritated** and often **infected**, resulting in **ulceration** of the **cornea**.
- The cause of the protruding eyes is edematous **swelling** of the retro-orbital tissues and degenerative changes in the extraocular **muscles**.

Malignant goiter (toxic)

- Usually, concomitant with **exophthalmos**.
- Results from the increased thyroid hormones secretion.
- Toxic because T_3 and T_4 levels are usually (not always) high (hyperthyroidism)

Hypothyroidism

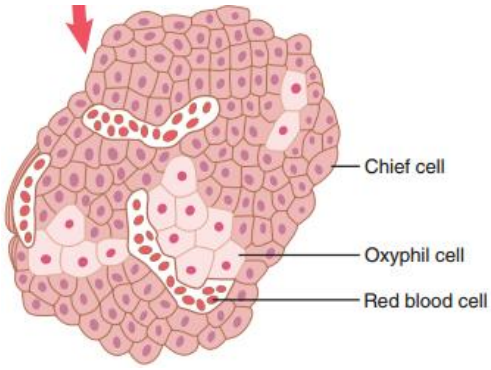
Cause	**T3,T4**	**TSH**	**Goiter**
Primary failure of thyroid gland	Low	High	Yes
Secondary to anterior pituitary failure	Low	Low	No
Iodine deficiency	Low	High	Yes

Hyperthyroidism

Cause	**T3,T4**	**TSH**	**Goiter**
Grave's disease (TSI)	High	Low	Yes
Secondary to excess anterior pituitary secretions	High	High	Yes
Thyroid tumor	High	Low	No

Parathyroid Glands

- **4** glands behind the thyroid gland.
- Each weighs **20** to **50** milligrams.
- Two types of cells:
  - **Chief** cells: secrete **most** of the PTH.
  - **Oxyphil** cells: retired chief cells, secrete **low** amounts of PTH.
- Develop at **5-14** weeks of gestation.



Parathyroid Hormone (PTH)

- **Polypeptide** hormone, 84 amino acids. (the first **34** form a functional hormone)
- **Short** half-life: **25** min.
- It increases plasma Ca^{2+} concentration to its normal level (10 mg/dl)
- **Essential** to life; its deficiency causes **severe** hypocalcemia and eventually death.
- It exerts its effects mostly by using **cAMP** second messenger and to a lesser extent **Ca^{2+}** second messenger or **direct** effects **without** the need of any second messenger.
- Parathyroid hormone related protein (**PTHRP**) is also secreted from the parathyroid glands and has a similar function to PTH.

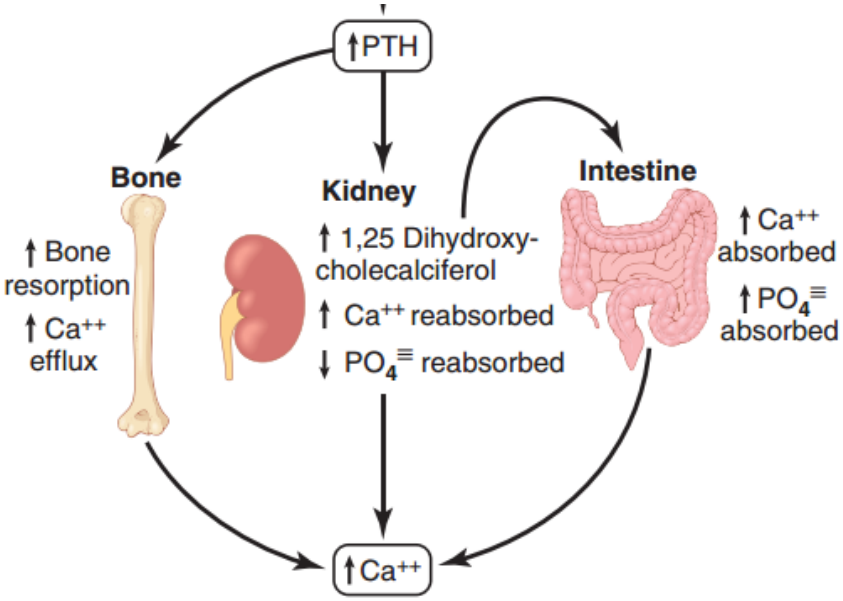
Parathyroid hormone secretion:

1) Ca^{2+} binds to calcium sensing receptor (**CaSR**) on the parathyroid glands cells.
2) CaSR activates **G** protein with an eventual increase in cytosolic **Ca^{2+}, IP3, DAG**.
3) This, unlike other glands, **decreases** PTH secretion.

- Low plasma Ca^{2+} level doesn't lead to the inhibition of PTH secretion.
- Other chemicals have a less important role in regulating PTH secretion
  - High Mg^{2+} , PO_4^{-3} **stimulates** PTH secretion
  - High vitamin D **inhibits** PTH secretion.

PTH effects

- **Increases plasma Ca^{2+} by** :
    - Increasing **bone resorption** by direct effects on osteoblasts and osteocytes (osteolysis; absorption of minerals **without** resorption of the bone's fibrous and gel matrix) and indirect effect on osteoclast.
    - Decreasing Ca^{2+} **excretion** by the kidneys.
- **Causes a net decrease in plasma PO_4^{-3} by**
    - Increasing its **excretion** by the kidneys.
    - Increasing bone **resorption**.
- Stimulates the formation of 1,25-dihydroxycholecalciferol in the kidneys.
- Increases reabsorption of Mg^{2+} , H^+.
- Decreases reabsorption of Na^+, K^+, amino acids.



Ca^{2+} roles in human body

- **Ca^{2+} plasma concentration is very strictly regulated.**
- **Its normal concentration range is 10-11 mg/dl.**
- Involved in excitation-contraction coupling in muscle cells.
- Serves as an intracellular signal for some Hormones and enzymes.
- Functions as a cofactor for many enzymes
- Involved in blood clotting process.
- Causes fusion of vesicles and secretion of their contents such as insulin and acetylcholine
- Constituent of the bones.
- PTH deficiency decreases

Hypocalcemia

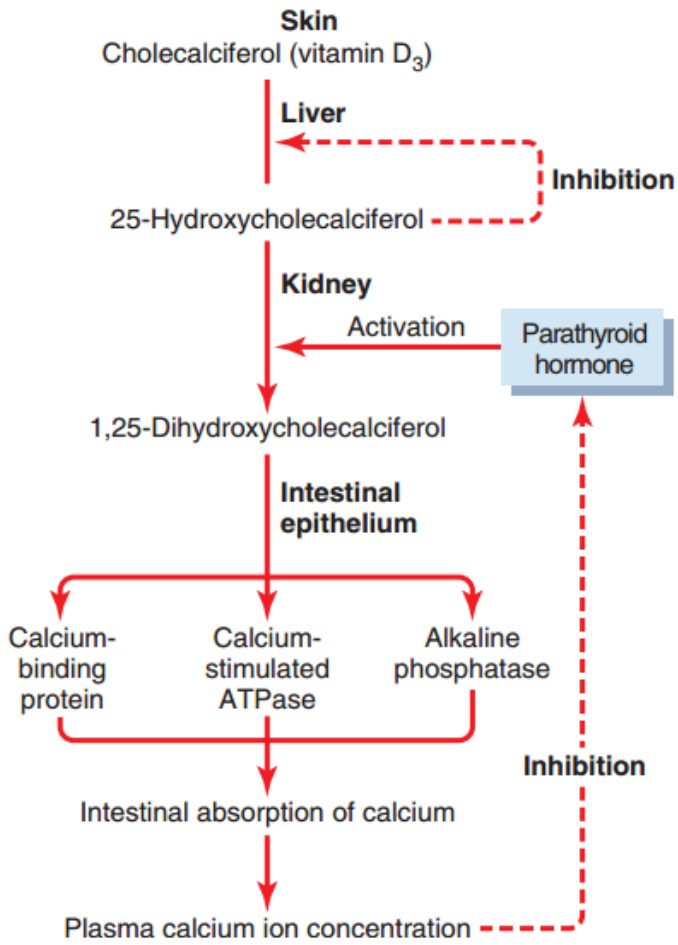
- PTH deficiency caused by **atrophy** of **removal** of the parathyroid glands.
- Decreased Ca^{2+} increases neuronal membrane permeability to **Na^{+}**.
- This causes continuous **depolarization** of the membranes and **spontaneous** generation of action potentials.
- This causes **tetanic** (permanent) muscle contraction.

Hypercalcemia

- Oversecretion of PTH caused by a **tumor** in the parathyroid gland.
- Increases Ca^{2+} mainly by resorption of the bones **matrix**; **not only minerals**, causing **osteitis fibrosa cystica** (fragility of the bones).

Vitamin D

- Many compounds belong to vitamin D family.
- Vitaminn D3 (**cholecalciferol**) is the most important.
- The dietary compound is vitamin D2 (**ergocalciferol**).



1) U.V rays from the sun convert **7-dehydrocholesterol** in the **skin** to **cholecalciferol** (vitamin D3).

2) In the **liver**, **cholecalciferol** is hydroxylated to form **25-hydroxycalciferol** which has negative feedback effect to inhibit this reaction.

3) In the kidney, 25 hydroxycalciferol is converted to **1,25-dihydroxycholecalciferol** and **24,25-dihydroxycholecalciferol** with different proportions depending on **Ca^{2+}** plasma concentration.

- If **Ca^{2+}** concentration is low, increased PTH levels causes the enzyme **1α-hydroxylase** to convert 25-

hydroxycalciferol to 1,25-dihydroxycholecalciferol which is the **most potent** form of vitamin D.

- If Ca^{2+} concentration is high, decreased PTH levels causes the enzyme **24-hydroxylase** to convert 25-hydroxycalciferol to 24,25-dihydroxycholecalciferol which is **1/20** as potent as 1,25-dihydroxycholecalciferol.

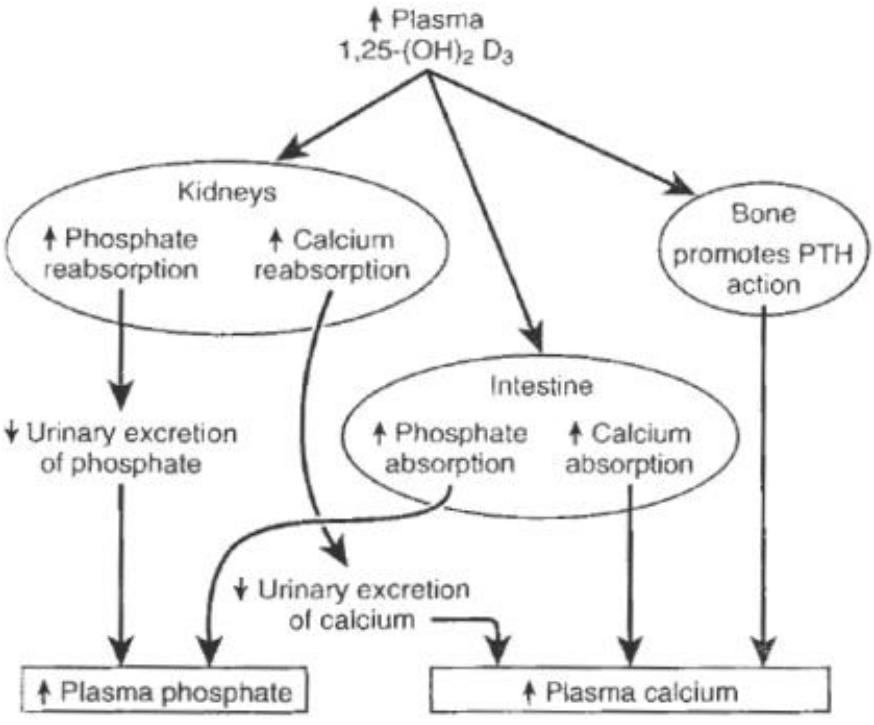
Note: cholecalciferol, 25-hydroxycholecalciferol (**1/1000** as potents as 1,25-hydroxycholecalciferol), 24,25-hydroxycholecalciferol (**1/20** as potents as 1,25-hydroxycholecalciferol), 1,25-hydroxycholecalciferol are all found in the plasma bound to proteins. Only the latter has a significant vitamin D effects; the others are almost **inactive**.

- Vitamin D3 is stored in **adipose** tissue.
- The accumulation of **fat**, especially in the abdomen, **decreases** the release of vitamin D3 which causes some problems affecting many tissues including the heart.

Effects of Vitamin D

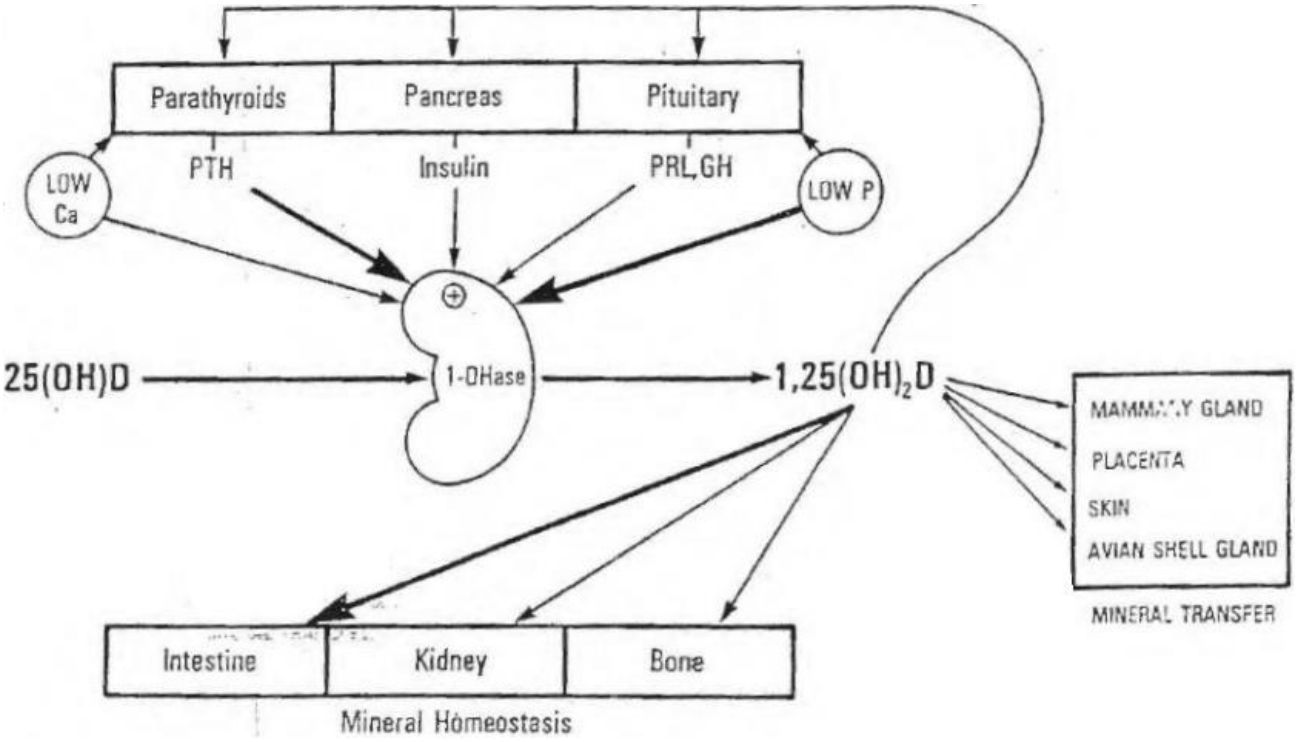
1. **Intestines**: increases Ca^{2+}, PO_4^{-3} absorption. (strong effect)
2. **Kidneys**: increases Ca^{2+}, PO_4^{-3} reabsorption. (weak effect)
3. **Bone**: promotes the action of PTH.

- Vitamin D has a **synergistic** effect with PTH since both increase Ca^{2+} plasma concentration.
- Normal amounts of vitamin D promote bone calcification by increasing Ca^{2+} intestinal absorption.
- High amounts of vitamin D promote bone resorption,
- In the absence of vitamin D, the effect of PTH in causing bone resorption is greatly reduced or even prevented.



Regulation of vitamin D synthesis

- The step catalyzed by **1α-hydroxylase** in the kidneys (coverts 25-dihydrocholecalciferol to 1,25-dihydrocholecalciferol) is stimulated by many factors.



Low Ca^{2+} **directly** affects the kidneys and also stimulates the secretion of **PTH**.

Low PO_4^{-3} **directly** affects the kidneys and also stimulates the secretion of prolactin (**PRL**) and growth hormone (**GH**)

PTH, GH, PRL, Insulin all stimulate the synthesis of the active vitamin D.

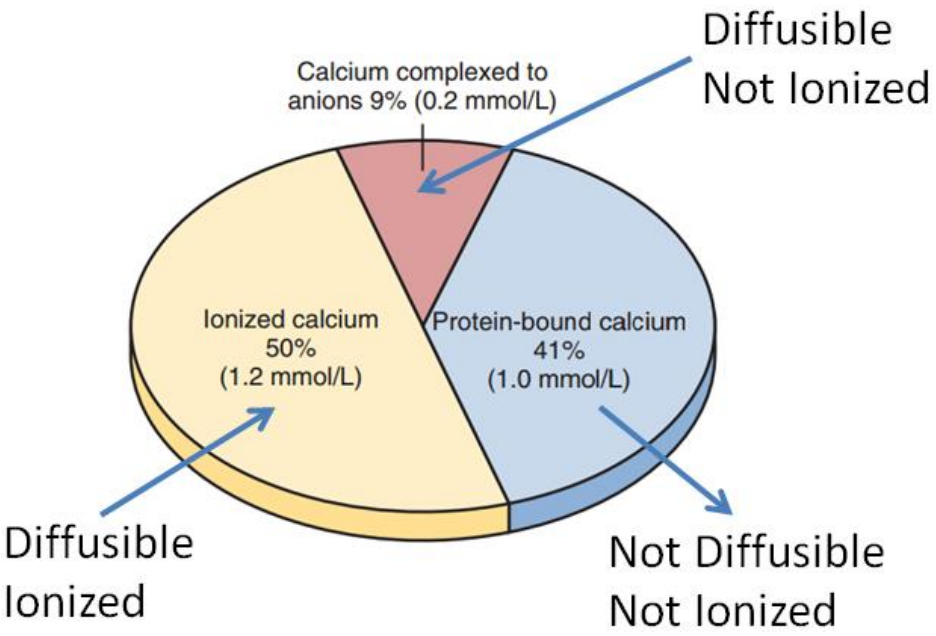
Of all these factors, the direct effect of low $\mathbf{PO_4^{-3}}$ on the kidneys and the effect of **PTH** (secondary to low Ca^{2+}) are considered the major stimulants.

Note: Vitamin D also affects mammary glands, placenta, skin and a

vian shell gland.

Note: Bone mass in men is higher than in women owing to the higher level of androgens in men.

- **99%** of the body's Calcium is stored in the bones.
- **85%** of the body's PO_4^{-3} is stored in bones.



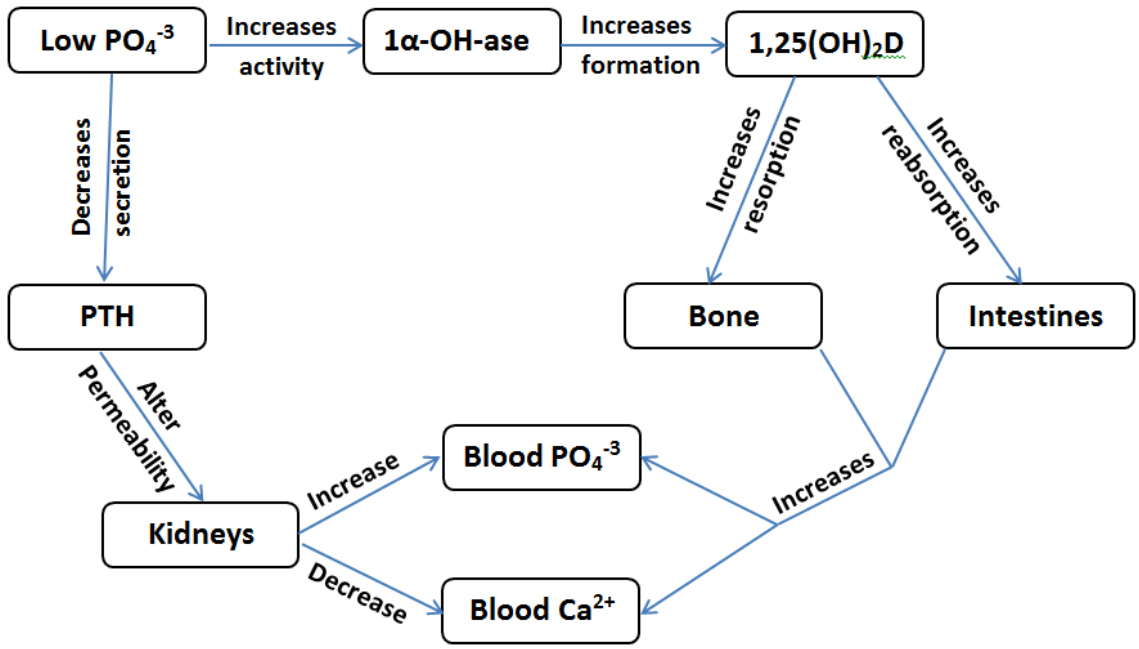
50% of the body's calcium is **ionized** (free; not bound to **anions** nor **proteins**) and **diffusible** through the capillaries

Only the ionized calcium can stimulate **PTH** secretion.

Effect of blood pH

- In **acidosis** (low blood pH), excess $\mathbf{H^+}$ binds to plasma proteins (albumin) leaving calcium in the form of free and **ionized**.
- In **alkalosis** (High blood pH), $\mathbf{H^+}$ doesn't bind to albumin leaving it to be **bound** to Ca^{2+} .This decreases the free ionized calcium and increases the protein-bound calcium.

Phosphate homeostasis



- Increased **PO_4^{-3}** stimulates **PTH** secretion to increase its **excretion** by the kidneys.
- Decreased **Po_4^{-3}** triggers the formation of 1,25-dihydroxycholecalciferol by increasing the activity of 1α-hydoxylase in the **kidneys**. This increases intestinal **absorption** of PO_4^{-3} and bone **resorption**.

Calcitonin

- **32** amino acids polypeptide. The active region is in the center.
- Secreted by the **parafollicular** cells (C cells) of the thyroid gland.
- Generally, it **antagonizes** the effects of **PTH**.
- It also acts as a **neurotransmitter** in the CNS.
- Secreted in response to high **Ca^{2+}** level.
- Degraded in the **liver** and the **kidneys** with a half-life of 30-60min.
- **Effects:**
- It inhibits bone **resorption** and **osteolysis**.
- It **inhibits** Ca^{2+} and PO_4^{-3} **reabsorption** (increases their excretion by the kidneys).
- It has an **opposite** effect to PTH in maintaining **Ca^{2+}** homeostasis.
- It has the **same** effect of PTH in maintaining **PO_4^{-3}** homeostasis.
- Excess calcitonin doesn't cause hypocalcaemia. Also, its deficiency doesn't cause hypercalcemia.These phenomena are not understood.
- A possible explanation is that **PTH** and **calcitonin counterbalance** the excess or deficient calcitonin.

Abnormalities of calcium homeostasis.

Rickets

- Children, since their **fat** stores are less than in adult, their vitamin D stores are **not sufficient** for long times.
- Rickets occurs in children who are not adequately exposed to the sun **OR** their dietary intake of vitamin D in insufficient.

Osteomalacia

- Rickets in **adults** is called osteomalacia.

- Less frequent than rickets, since calcium **isn't** as needed in adults as in children for bone mineralization.
- **Steatorrhea** (presence of unabsorbed **fat** (including vitamin **D**) in the **feces**) causes vitamin D deficiency and **osteomalacia**. Ca^{2+} binds to these fats and is **also** excreted in the feces.
- Steatorrhea itself is usually caused as a result of **prolonged diarrhea** in adults.

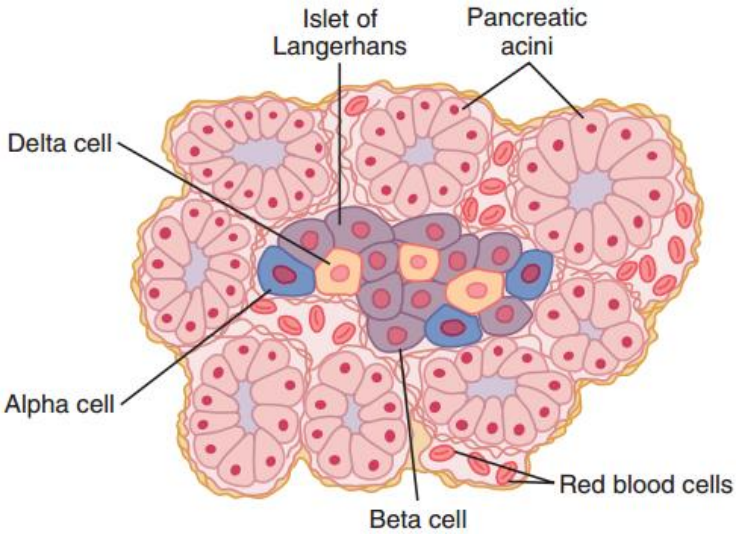
Osteoporosis

- The most **common** of all bone diseases especially in old women.
- In contrast to rickets and osteomalacia in which **only bone calcification is reduced without affecting the fibrous matrix (proteins), in osteoporosis, bone is normally calcified but the matrix (bone mass) is affected as a result of reduced osteoblastic activity and increased osteoclastic activity**.
- **Causes:**
  - Severe malnutrition which decreases fibrous proteins synthesis.
  - Physical inactivity.
  - Decreased vitamin C intake which results in reduced matrix deposition by osteoblasts.
  - Postmenopausal women because of diminished estrogens which inhibit osteoclasts number and activity.
  - Old age because of reduced GH and growth factors.
  - Cushing's syndrome in which excess cortisol reduces proteins deposition
  - Acromegaly.
- **Treatment:**
  - Estrogens for females (not males because it's converted to testosterone)
  - Vitamin D and Ca^{2+} administered before age 30 to increase peak bone mass.

Note: administration of steroids such as cortisol by athletes to increase muscular mass is dangerous because these athletes may become homosexual.

The pancreas

- **2 parts:**
  - **Exocrine**:
    - Pancreatic acini.
    - Secrete enzymes and ions.
  - **Endocrine**:
    - Islets of Langerhans.
    - Secrete hormones.
    - Many cell types different in morphology and staining.

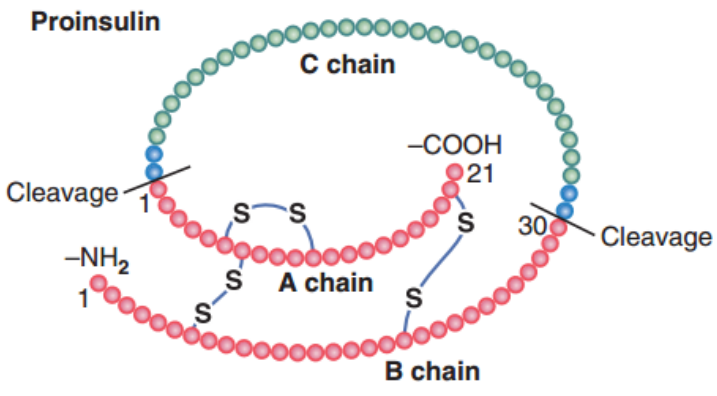


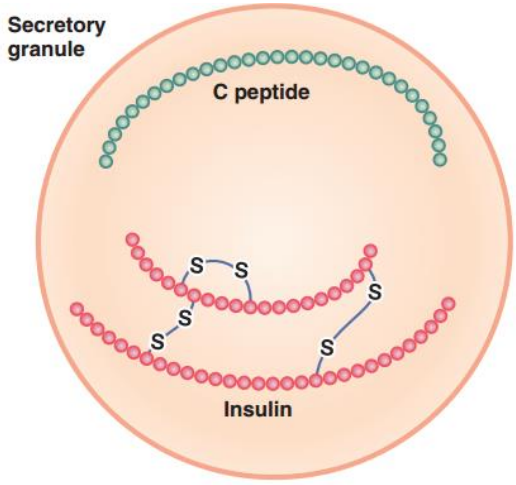
Cell type	Percentage of all cells	Products secreted
Alpha	20	Glucagon, Proglucagon
Beta	75	Insulin, Proinsulin, C peptide, Amylin
Delta	4	Somatostatin
PP or F	1	Pancreatic polypeptide, Ghrelin

Insulin

Synthesis

1) mRNA is translated on bound ribosomes in beta cells to produce **preproinsulin**.
2) Cleaved in ER to form **proinsulin**.
3) 95% is again cleaved in Golgi to form **Insulin** and the cleaved chain (**C peptide**)
4) Insulin and C peptide are packaged in the secretory granules and secreted. only 5% of the secreted product is ProInsulin.

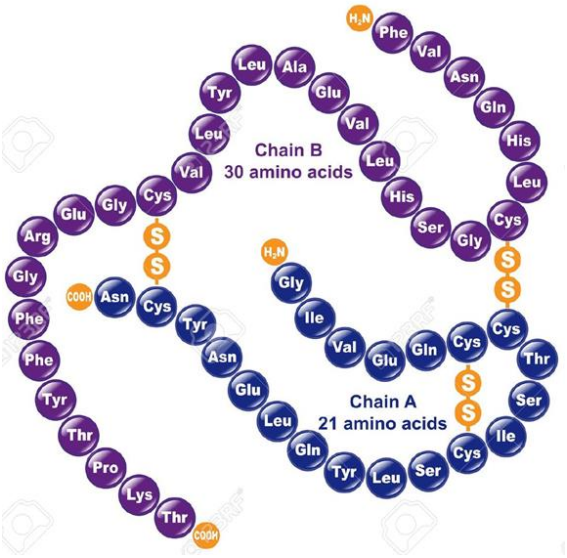




- Proinsulin has **no** insulin activity. (It's, however, said to have 10% of insulin activity).
- **C peptide significance:**
- Insulin and C peptide are secreted in **equimolar** amounts.
- Activates 2 enzymes; Na^+ / K^+ ATPase and endothelial nitric oxide synthase.
- C peptide levels can be measured in insulin-treated diabetic patients to determine how much of their own natural insulin they are still producing.
- 50-60% of the insulin secreted by the pancreas is extracted by the liver, and doesn't reach the systemic circulation but it doesn't extract the C peptide. The amount of insulin secreted by the pancreas is obtained by measuring the level of C peptide not insulin.

Chemistry and Kinetics

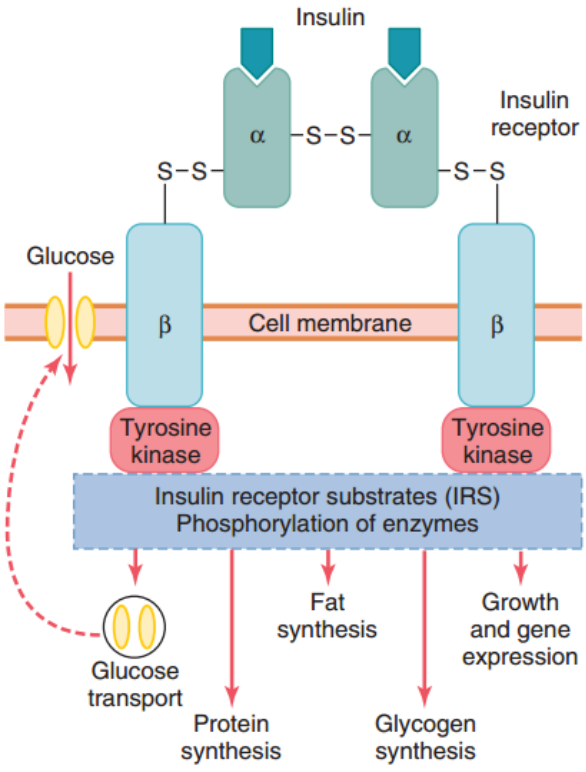
- Small protein; 2 amino acid chains; A and B connected by S-S bonds.
- Both chains are important for its function.
- Half-life: 6 min.
- Cleared within 15 min.
- Degraded by insulinase mainly in the liver, to a lesser extent in the kidneys and muscles, and slightly in most other tissues.



Mechanism of Action

1) Insulin binds with alpha subunit of its receptor outside the cell membrane.
2) Beta subunit witch penetrate through the cell membrane become autophosphorylated.
3) Local tyrosine kinase becomes activated. Tyrosine kinase phosphorylates other enzymes activating some and inactivating the others.

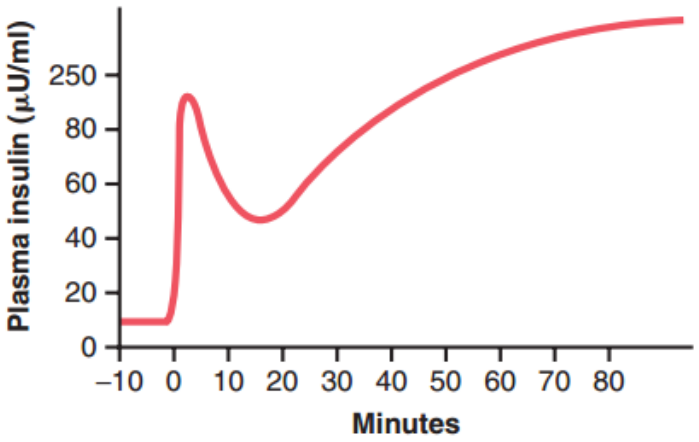
- Insulin is also found to activate phospholipase C with an increase in IP3 and DAG which promote amino acids uptake by cells and protein synthesis. This effect stimulates growth, synergizing with GH.



Secretion

- Its secretion is associated with **energy** abundance.
- The source of energy is **not** necessarily glucose; it could be amino acids or fatty acids.
- Glucose is the most important because beta cells' membranes are rich with glucose transporter 2 (GLUT 2).

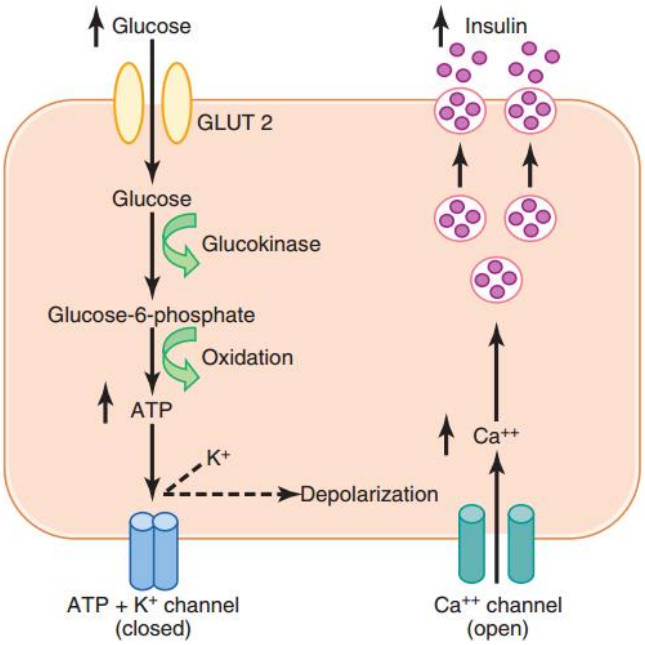
– At fasting glucose level, 90mg/dl, the rate of insulin secretion is minimal.
– Insulin level increases almost 10-fold within 5 minutes (presynthesized insulin is secreted)
– Insulin concentration decreases halfway back toward normal in another 10 minutes. (**Presyntesized** insulin runs out)



– After 15 minutes, insulin secretion rises a to reach its maximium in 2 to 3 hours (**Newly** synthesized insulin is secreted)

- **Mechanism:**

1) Once inside the beta cell, glucose is phophorylated by glucokinase; the rate limiting step.
2) Glucose 6-phosphate is oxidized to form ATP.
3) ATP inhibits ATP-sensitive K+ channels closing them.
4) Cell membrane becomes depolarized.
5) Voltage-gated calcium channels open.
6) Calcium enters and stimulates fusion of insulin containing vesicles with the membrane and secretion of insulin.



- Insulin secretion rate reaches its maximum at glucose level of 300-400 mg/dl and it almost completely diminishes at glucose level of 50 mg/dl.

- **Regulation**

Stimulants	Inhibitors
Energy abundance	Low energy
High glucose, amino acids, fatty acids level	Low glucose, amino acids, fatty acids level
Parasympathetic stimulation	Somatostatin
Beta adrenergic stimulation	Alpha adrenergic stimulation
GI hormones, gluagon, GH, cortisol	Leptin

- **Effects**
  - Stimulates glucose uptake by increasing the number and activity of GLUT especially GLUT4. The excess glucose is stored as glycogen in the muscles and the liver.
  - Stimulates amino acids uptake and protein synthesis.
  - Stimulates fat synthesis.
  - Stimulates growth by increasing protein synthesis and induction of gene transcription
  - Inhibits gluconeogenesis.
  - Stimulates cells uptake of potassium and phosphate ions. Maintaining normal K^+ level is essential for normal action potential generation and thus, heart function. This is impaired in diabetic patients.

- **Notes:**
  - Normal Plasma glucose concentration is 90 mg/dl.
  - Glucose entry to the brain, kidney tubules, intestinal mucosa and red blood cells doesn't require insulin.
  - The tissues most importantly affected by insulin are the liver, adipose tissue, muscles.
  - Glucose level is maintained by:
    - Short term regulation: by insulin and glucagon.
    - Long term regulation: by corticosteroids, GH, epinephrine, thyroid hormones.
  - The only hypoglycemic hormone is insulin.
  - Many hormones are hyperglycemic. Glucagon is the most important.
  - Cortisol permits glucagon action in stimulating gluconeogenesis.

	Glucagon	Epinephrine	Cortisol	GH	T3
Glycogenolysis	YES	YES			YES
Gluconeogenesis	YES	YES	YES	YES	YES
Lipolysis	YES	YES	YES	YES	YES
Blockade of glucose uptake		YES	YES	YES	

- Normally, insulin stimulates glucose uptake by almost all tissues:
  - 5% to liver.
  - 30 to 40% to adipose tissue.
  - Low concentration to muscles and other tissues.
- In insulin deficiency:
  - Plasma glucose level rises (300 mg/dl)
  - Glucose isn't transport to adipose or muscle tissues
  - Glucose output from the liver is greater than glucose input.
  - Brain is not affected unless glucose level rises too high (remember, the brain is insulin-independent)
  - High concentration of glucose transferred to kidneys causing glycosuria (Note: glucose is undetectable in urine as long as blood glucose level is lower than the renal threshold (180mg/dl.

Diabetes Mellitus (DM)

- Two types of DM:

1. Type 1 DM (Insulin-dependent, Juvenile):
   - Lack of insulin secretion.
   - 5% of diabetic patients
2. Type 2 DM (non-insulin-dependent, adult):
   - Decreased sensitivity to insulin (insulin resitance)
   - 95% of diabetic patients

Feature	Type 1	Type 2
Age at onset	Usually <20 yr	Usually >30 yr
Body mass	Low (wasted) to normal	Visceral obesity
Plasma insulin	Low or absent	Normal to high initially
Plasma glucagon	High, can be suppressed	High, resistant to suppression
Plasma glucose	Increased	Increased
Insulin sensitivity	Normal	Reduced
Therapy	Insulin	Weight loss, thiazolidinediones, metformin, sulfonylureas, insulin

- Polyuria, dehydration, increased thirst are classic symptoms of diabetes:
  - Glucose does not diffuse to cells increasing osmotic pressure in the extracellular fluids which causes osmotic transfer of water out of the cells.

- Glucose in the renal tubules greatly decreases tubular reabsorption of fluid (renal diuresis).

DM and Fat Metabolism

- Adipocytes express the enzyme hormone sensitive lipase which, when active, cleaves triglycerides (TG) stored into glycerol and free fatty acids (FFAs).
- Insulin doesn't only stimulate fat synthesis; it also inhibits fat breakdown by inhibiting hormone sensitive lipase in adipocytes.
- In diabetic patients, the increase in fat breakdown and decrease in fat synthesis greatly raise FFAs concentration in the blood.
- The increased metabolism of these FFAs produces high amounts of ketone bodies (causing ketosis) of which 2 are acids and also cause acidosis. These ketone bodies are acetone, acetoacetic acid and β-hydroxybutyric acid.

DM and Protein Metabolism

- Increased protein catabolism and decreased protein synthesis leads to greatly increased amino acids concentration in the blood. These are used as:
  1. Substrates to generate energy (ATP).
  2. Substrates for the production of glucose by gluconeogenesis. This further worsens the situation by further increasing blood glucose level.
- In patients with DM1 who don't receive the appropriate treatment, energy generation is almost totally dependent on protein catabolism. This causes marked decrease in body mass despite increased consumption of food.

Coma and Glucose level

- Coma related to glucose level can be a final result of several events:
  1. Hypoglycemia: glucose level below 40 mg/dl.
     - Patients with DM1 treated with high dose of insulin may experience hypoglycemic shock and coma.
  2. Hyperglycemia: diabetic coma as a result of:
     a. Severe acidosis
     b. Hyperosmolar plasma
     c. Lactic acid accumulation
     d. Brain edema in children.

Treatment of DM

- Type 1: exogenous insulin administration.
- Type 2: 3 stages:
    1. Dieting and exercise to reduce weight and increase sensitivity to insulin.
    2. Drugs:
        - Insulin sensitizers: increase tissues sensitivity to insulin
        - Insulin secretagogues: Increase pancreatic insulin secretion. (e.g. sulfonylureas)
        - Others suppress liver glucose production. (e.g. metformin)
    3. Exogenous Insulin administration.

Complications of Untreated DM

- Cardiovascular diseases (CVDs) are the most common being the cause of death of 65% of diabetic patients. The prevalence of CVDs in diabetic patients is 2-4 times greater than in non-diseased population.
- The risk of cancer is increased in diabetic patients.
- Prolonged diuresis and polyuria exhaust the kidneys leading to renal failure.

Obesity

- Obesity in children results from an increase the size and number of fat cells while in adults, only the size is increased.
- 3 Obesity indicators:
    1. Body mass should equal height (cm) – 100 in males and height (cm) – 105 in females.
    2. Waste circumference should be less than half the height.
    3. BMI= weight/height^2 :

Glucagon

- A protein secreted from α cells of the pancreas, transferred via the portal circulation to the liver where it exerts most of its effect and then reaches other tissue to control their metabolism.

- Together with insulin, it's involved in the short term regulation of blood glucose level. It antagonizes the effect of insulin.
- Amino acids released after digestion of protein rich meals appear to be the major stimulant of glucagon secretion.

Carbohydrate metabolism

- Stimulates glycogenolysis in the liver and muscles.
- Stimulates gluconeogenesis in the liver.

Lipid metabolism

- Stimulates lipolysis in adipose tissues. This also increases ketogenesis.

Protein metabolism

- Unlike insulin, it promotes protein catabolism (especially in pharmacological concentrations) and like insulin, it promotes amino acids uptake by cells. However:
    - In case of insulin stimulation, these amino acids are then used to synthesize proteins.
    - In case of glucagon stimulation, these amino acids are then used as substrates for gluconeogenesis.

1) One of the following is correct regarding classis hormones:
   a) They are secreted from endocrine glands into a duct.
   b) They are usually secreted in the blood to affect nearby cells.
   c) Acetylcholine is a good example.
   d) Most are polypeptide hormones.
   e) They can affect muscles to cause their contraction

2) Hormone X binds to an intracellular receptor of a target cell to induce lipolysis and reduce glucose uptake. One of the following doesn't correctly describe X.
   a) X is likely to activate a G protein coupled receptor
   b) X, most probably, induces transcription of specific regions of DNA.
   c) X has pleotropic effects.
   d) X, most probably, affects many types of cells.
   e) X must be bound to proteins in the plasma.

3) Binding of the hormone Y induces a cellular process 3-fold its induction of the same process after prolonged exposure of the cell to hormone Z. One of the following correctly describes Y.
   a) Y has desensitizing effects of the cell to Z.
   b) Binding of Y causes homologous desensitization of the cell.
   c) Z antagonizes the effects of Y.
   d) Z decreases the number of receptors of Y on the cell.
   e) Both c+d are correct.

4) One of the following hormones doesn't bind to a membrane receptor.
   a) Thyroxine.
   b) Norepinephrine
   c) Epinephrine
   d) Thyroid stimulating hormone
   e) Glucagon

5) Secretion of a hormone further increased its secretion in the blood. One of the following correctly describes the hormone:
   a) The stimulus-response is Hormone-Hormone.
   b) It's possible that the affinity of the receptor of the hormone is decreased.
   c) It's possible that the hormone exhibits positive feedback mechanism.
   d) Both a+b are correct.

e) All a+b+c are correct.

6) Hormone A inhibits the release of the hormone that affected the gland which secreted it:

a) This is an example of the positive feedback mechanism.
b) This is an example of short loop feedback.
c) It's possible that Hormone A is oxytocin.
d) The gland that secreted the hormone A possesses the receptor of the hormone A.
e) More than one is correct.

7) Knowing that ACTH is necessary for the secretion of aldosterone. One of the following is true:

a) The interaction is called synergism.
b) To secrete more amounts of aldosterone, more ACTH is required.
c) ACTH is sufficient to cause aldosterone secretion.
d) All are correct.
e) Nothing is correct

8) One of the following is not a characteristics of peptide hormones:

a) They usually increase intracellular second messengers' concentrations such as cAMP, Ca^{2+}, PI3, DAG.
b) Their action is always fast and prolonged.
c) They can't cross cell membranes.
d) Some are glycoproteins.
e) They play a very important role in the growth process.

9) One of the following is true about the pituitary gland and its hormones:

a) The posterior pituitary synthesizes 2 hormones, oxytocin and ADH.
b) Some neurons in the hypothalamus secrete neurohormones directly into the blood.
c) ADH is secreted in response to decreased extracellular fluid osmolarity.
d) Increased Na^{+} reabsorption caused by ADH increases blood pressure.
e) More than one is correct.

10) One of the following is not correct regarding the anterior pituitary and the hypothalamus:

a) Growth hormone and prolactin are both secreted from somatotropes
b) The only cell type of the anterior pituitary that secretes two major hormones is gonadotropes.
c) The only hypothalamic hormone which has an inhibitory effect is PIH.
d) Hormones from the hypothalamus reach it by either long or short portal vessels, depending on the rapidity needed for the effects.
e) All are correct

11) One of the following is not correct regarding parturition and uterine contractions:

a) Estrogens and not oxytocin are responsible for the initiation of parturition.
b) Estrogens stimulate oxytocin secretion.
c) Cervical stretching stimulates oxytocin secretion
d) Prostaglandins stimulate uterine contractions.
e) All are correct.

12) One of the following chemicals doesn't play a role in the growth process:

a) Insulin
b) Somatomedin C
c) Aldosterone
d) Thyroxine
e) Cortisol

13) One of the following is not correct about growth hormone:

a) Spares proteins.
b) Increases lipolysis.
c) Excess may cause ketosis and acidosis.
d) Inhibits release of insulin from the pancreas.
e) All are correct.

14) One of the following statements is not true regarding growth hormone:

a) Has a synergistic effect with insulin.
b) Its secretion is increased after a carbohydrate-rich meal.
c) Its secretion is inhibited in diabetic patients.
d) Somatomedins inhibit its secretion.
e) Its secretion is increased in fasting individuals and after a strenuous exercise.

15) One of the following statements is incorrect regarding ACTH:

a) It has an important role in stimulation of the secretion of adrenal androgens, especially after puberty.
b) α subunit is necessary for its activity.
c) Its target zone is zona fasciculata.
d) Its secretion is inhibited by cortisol
e) All are correct.

16) Cortisol doesn't have an important contribution to the mineralocorticoid activity because:

a) Cortisol can't bind to MR receptor.
b) Cortisol concentration in the blood is lower than aldosterone.
c) Kidney's epithelial cells convert cortisol to corticosterone.
d) Cortisol can't enter the cell to bind the receptor.
e) None of the above is correct.

17) A good indicator of 11β-hydroxylase (converts 11-deoxycortisol to cortisol) deficiency is:

a) Increased level of corticosterone.
b) Increased level of aldosterone.
c) Decreased level of androgens.
d) Increased level of deoxycortisol.
e) More than one is correct.

18) One of the following is correct about cortisol:

a) Its effects in protein and fat metabolism aren't as important as its effects on carbohydrates metabolism.
b) Only 6% of the plasma cortisol is free.
c) Has a relatively long half-life.
d) Its level reaches its peek at 12:00 PM.
e) Important during fasting but not essential in fetal life.

19) One of the following is not an effect of cortisol:

a) Potentiates the effects of glucagon and epinephrine.
b) Increases hepatic protein mobilization.
c) Conserves glycogen stores.
d) Responds to many types of stresses.

e) All are correct.

20) One of the following doesn't stimulate aldosterone secretion at all:

a) Angiotensin 2 and 3.
b) Decreased Na^+ delivered to the kidneys.
c) Increased intracellular K^+ concentration.
d) ACTH
e) All are correct.

21) One of the following is not correct about adrenal androgens and estrogens:

a) DHEA is a weak androgen.
b) DHEA is secreted from zona reticularis.
c) They are the main responsible for female sexual characteristics
d) A tumor in the adrenal cortex may cause their oversecretion.
e) The most potent androgen is testosterone

22) One of the following is not correct regarding the regulation of thyroid hormones secretion:

a. Lactotropes possess the receptor of TRH.
b. TRH increases the bioactivity of TSH by increasing Ca^{2+} concentration in thyrotropes.
c. β Subunit of TSH is the active one but α subunit is necessary for TSH function.
d. TSH increases Ca^{2+} in thyrotropes to stimulate thyroid hormones secretion.
e. Dopamine inhibits thyroid hormones secretion.

23) One of the following is not correct regarding thyroid hormones synthesis:

a. MIT and DIT are covalently coupled to form active T3 ready to function.
b. Thyroglobulin is glycosylated in golgi.
c. The basolateral membrane of tyrotropes is rich in Na^+/I^- symporter.
d. In these cells, iodide is bound to tyrosyl residues of thyroglobulin.
e. More than one is incorrect.

24) One of the following is correct regarding thyroid hormones:

a. Both T3 and T4 have a negative feedback effect on the hypothalamus and the pituitary gland.
b. T3 can be converted to T2 which is totally inactive.

c. T3 is secreted in much higher amounts than RT3
d. 75% of T3 is obtained from T4 rather than from the thyroid gland.
e. More than one is incorrect.

25) A patient with low thyroid binding protein level in the blood would show all of the following except:
a. Low TSH level in the blood.
b. Inhibited thyroid hormones secretion.
c. Not significantly affected thyroid hormones transfer in the blood since most of them are bound to albumin.
d. Decreased half-life of T3.
e. The patient wouldn't show any the above mentioned observations.

26) One of the following is not correct regarding panhypopituitarism:
a. A tumor that causes oversecretion of pituitary hormones may eventually causes panhypopituitarism.
b. GH deficiency doesn't affect mental abilities but causes the development of all body's parts in inappropriate proportions.
c. FSH and LH deficiencies decrease libido in both males and females.
d. TSH deficiency increases weight gain.
e. A+C are both incorrect.

27) One of the following is correct regarding dwarfism
a. Moderate anterior pituitary deficient patients are dwarfs.
b. Thyroid hormones deficient dwarfs are mentally retarded.
c. Iodine deficiency in children causes endemic cretinism.
d. In cretinism, patients look thinner than usual.
e. More than one is correct.

28) One of the following is correct about goiter:
a. In idiopathic goiter, TSH secretion is increased and thyroiditis is observed.
b. In benign goiter, TSH is deficient and T3 level is usually decreased.
c. In iodine deficient patients, thyroglobulin secretion into the colloid is greatly decreased.
d. Anterior pituitary failure is one of the causes of goiter.
e. In patients with toxic goiter, exophthalmos is usually observed.

29) One of the following is correct regarding parathyroid glands:

a. Ca^{2+} activates calcium sensing receptor on their cells.
b. Vitamin D inhibits PTH secretion.
c. PO_4^{-3} in the blood stimulates PTH secretion.
d. Increased cytosolic Ca^{2+} inhibits PTH secretion.
e. All are correct.

30) One of the following is correct regarding the effects of PTH:

a. PTH deficiency causes osteitis fibrosa cystica.
b. PTH has an opposite effect to vitamin D in maintaining $PO4^{-3}$ homeostasis.
c. Physiologic increase in PTH level directly increases osteoclastic activity and osteolysis
d. PTH promotes the conversion of 25-hydroxycholecalciferol to 24,25-dihydroxycholecalcifrol.
e. PTH increases excretion of H^+.

31) One of the following is not correct about vitamin D:

a. Insulin, prolactin, PTH and GH all stimulate the synthesis of active vitamin D.
b. Low PO_4^{-3} has an important direct effect in activating 1α-hydroxylase.
c. Low Ca^{2+} has an important direct effect in activating 1α-hydroxylase.
d. Its effect to increase Ca^{2+} and PO_4^{-3} reabsorption by the kidneys is essential to increase their levels in the blood.
e. More than one is incorrect.

32) One of the following regarding calcium level is not correct:

a. Calcium bound to proteins is neither ionized nor diffusible through the capillaries.
b. In alkalosis, bound calcium is increased resulting in increased PTH secretion.
c. The final effect of low $PO4^{-3}$ level on the intestines counterbalances its final effect on the kidneys in maintaining Ca^{2+} level.
d. All are correct.
e. All are incorrect.

33) One of the following is correct about calcitonin:

a. Excess calcitonin causes hypocalcemia.
b. It has the same effect of PTH in maintaining PO_4^{-3} homeostasis.
c. It decreases Ca^{2+} level in the blood.

d. B+C are both correct.
e. A+B are both correct.

34) One of the following is not correct regarding the abnormalities of calcium homeostasis:

a. Children whose dietary intake of vitamin D is adequate are not susceptible to develop rickets even if they are poorly exposed to sun.
b. Chronic Diarrhea may cause osteomalacia because fat is bound to calcium and are both excreted.
c. Bone matrix in rickets and osteomalacia is not that affected.
d. In osteoporosis, osteoclasts activity is increased but more importantly, osteoblast activity is greatly reduced.
e. Vitamin D and Ca^{2+} supplements are not as effective in treating osteoporosis as in its prevention.

35) One of the following is correct about insulin and its precursors:

a. Preproinslin contains the C peptide which is cleaved to form proinsulin.
b. Insulin secreted is accompanied with the C peptide in the same secretory granules.
c. C peptide has no physiologic effect.
d. Insulinase cleave proinsulin to form insulin.
e. More than one is correct.

36) One of the following is correct regarding insulin secretion:

a. Without GLUT found in beta cells' membranes, glucose doesn't enter and insulin is not secreted.
b. After 15 minutes of carbohydrates consumption, insulin level returns back to normal.
c. ATP inhibits ATP-sensitive K+ channels in beta cells.
d. Cortisol stimulates insulin secretion because of its diabetogenic effect.
e. More than one is correct.

37) One of the following is not an effect of insulin:

a. Stimulates cells uptake of potassium and phosphate ions.
b. Stimulates growth by increasing protein synthesis and induction of gene transcription
c. Stimulates glucose uptake by the brain.

d. Stimulates amino acids uptake to be used as substrates for gluconeogenesis.
e. More than one is not an effect of insulin.

38) One of the following is a common feature of the two types of DM:

a. Glucagon concentration is high
b. Occur in old ages
c. Renal diuresis and reduced bodyweight.
d. Intracellular glucose concentration is high.
e. More than one is correct.

39) One of the following is true about diabetic patients:

a. The enzyme hormone sensitive lipase is always inhibted.
b. Severe ketosis may lead to hypoglycemic coma.
c. Administration of insulin is the first line therapy.
d. Increased fatty acids utilization causes acetone to be breathed out.
e. Renal failure is an early symptom of the disease.

40) One of the following is correct about glucagon:

a. It's the only hyperglycemic hormone in the body.
b. High amino acids level stimulates its secretion.
c. It stimulates glycogenesis.
d. Its effect in stimulating gluconeogenesis is synergized by cortisol.
e. In inhibits lipolysis and ketogenesis.

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
D	A	D	A	E	B	E	B	B	B	B	C	D	B	A	C	D	C	B	C
21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40
C	D	E	C	C	B	E	A	E	B	E	B	D	A	B	E	E	A	D	B