جمهورية العراق/وزارة التعليم العالي والبحث العلمي
الجامعة التقنية الوسطى
كلية التقنيات الصحية والطبية/بغداد
قسم المختبرات الطبية

الحقيبة الدراسية لمادة علم الغدد الصماء السريرية /المرحلة الثالثة/الكورس الثاني /CLINICAL ENOCRINOLOG

اعداد الحقيبة : أ.م.د.هدى فرحان احمد أ.م.د.احمد سعدي حسن

اسم المادة	لغة التدريس	السنة الدراسية	عدد الساعات الاسبوعية			
			نظري	عملي	المجموع	عددالوحدات
علم الغدد الصماء السريرية	الانكليزية	الثالثة	2	4	6	4
Clinical endocrinology		الكورس الثاني				

Second Semester (Clinical endocrinology)	
WEEK	**COURSE TOPICS**
1	Introduction to Endocrinology and types of glands, Definition of Hormones, Similarities and Dissimilarities of Hormone and Enzyme. Classification of Hormones, Factors Regulating Hormone Action and Regulation of hormones secretion.
2,3	MECHANISM OF ACTION OF HORMONES: 1-Interaction with nuclear chromatin (nuclear action). 2- Membrane receptors. 3-Stimulation of enzyme synthesis at the ribosomal. 4- Direct activation at the enzyme level. 5-c-AMP and hormone action. 6- Role of polyphosphoinositol and diacylglycerol in hormone action. 7-Role of calcium in hormone action. 8-Role of c-GMP in hormone action. 9- Role of phosphorylation of tyrosine kinase
4	The Hypothalamus releasing factors
5	The pituitary anterior gland
6	The Melanocyte-Stimulating Hormone (MSH) produced by middle (intermediate) lobe The Posterior Pituitary gland
7,8	The Thyroid gland
9	The Parathyroid glands
10	The Pancreas gland
11,12	The Adrenal glands
13	The Gonadal hormones
14,15	Several other glandular tissues are considered to secrete hormones, viz.:(*JG cells of kidney, Thymus, Pineal gland and GI tract.*

الجامعة التقنية الوسطى
كلية التقنيات الصحية والطبية بغداد
قسم المختبرات الطبية/ المرحلة/ الثالثة
المادة: علم الغدد الصماء السريرية(Clinical Endocrinology)

Title: **العنوان:**

L 1 (INTRODUCTION TO ENDCRINOLOGY)

Name of the instructor: **اسم المحاضر:**

Assist.prof.Dr. Huda Farhan Ahmed
Assist.prof.Dr. Ahmed Saadi Hassan

Target population: **الفئة المستهدفة:**

Students of the third stage of medical laboratories

Introduction: المقدمة:

Most glands of the body deliver their secretions by means of ducts. These are called **exocrine glands.** There are few other glands that produce chemical substance that they directly secrete into the bloodstream for transmission to various target tissues. These are ***ductless or endocrine glands. The***

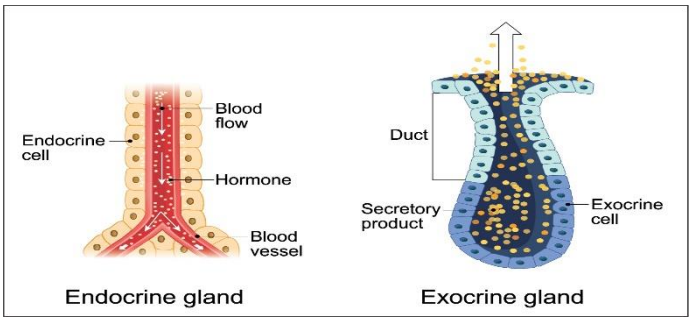
Pretest: الاختبار القبلي:

Define the hormones.

Scientific Content: المحتوى العلمي:

Introduction

Most glands of the body deliver their secretions by means of ducts. These are called **exocrine glands.** There are few other glands that produce chemical substance that they directly secrete into the bloodstream for transmission to various target tissues. These are ***ductless or endocrine glands. The secretions of endocrine glands are called as hormones.***



Definition of Hormones

It is ***a chemical substance which is produced in one part of the body, enters the circulation and is carried to distant target organs*** and ***tissues to modify their structures and functions.***

Hormones are strictly speaking stimulating substances and act as body catalysts. The hormones catalyse and control diverse metabolic processes, despite their varying actions and different specificities depending on the target organ.

Similarities of Hormone and Enzyme

The hormones have several characteristics in common with enzymes:

• They act as body catalysts resembling enzymes in some aspect.
• They are required only in small quantities.
• They are not used up during the reaction.

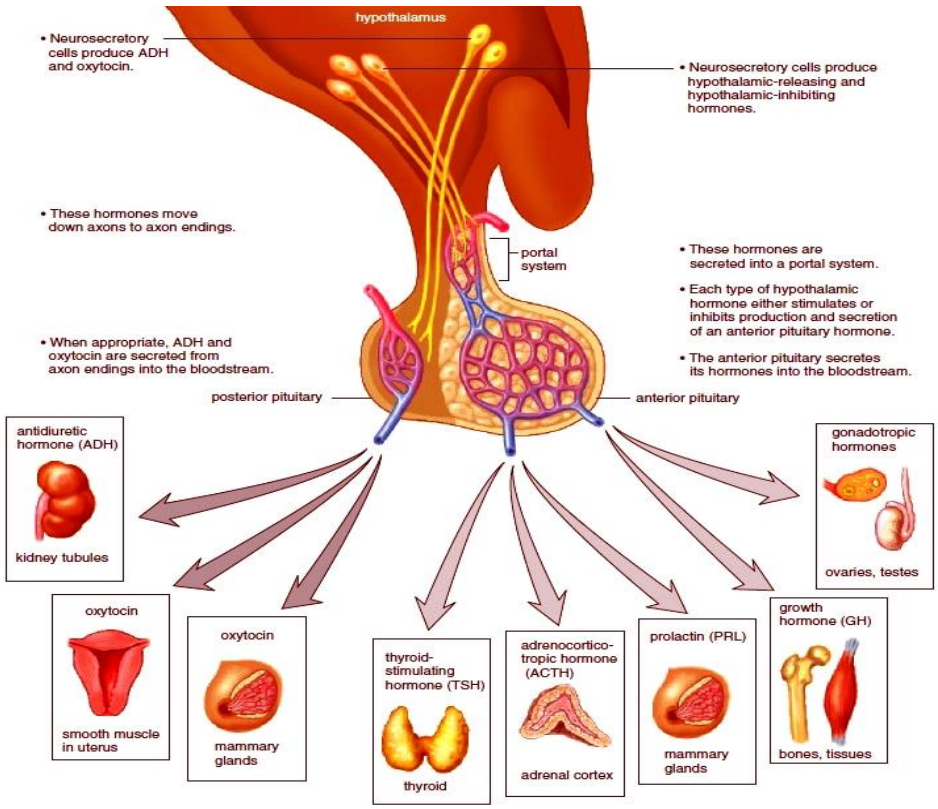
Dissimilarities of Hormone and Enzyme

They differ from enzymes in the following ways:

• They are produced in an organ other than that in which they ultimately perform their action.
• They are secreted in blood prior to use.
• Thus, the circulating levels of hormones can give some indication of endocrine gland activity and target organ exposure. Because of the small amounts of the hormones required, blood levels of the hormones are extremely low. In many cases it is ng/µg or mIU, etc.
• Structurally they are not always proteins. Few hormones are protein in nature, few are small peptides. Some hormones are derived from amino acids while some are steroid in nature.

The major hormone secreting glands are:

• Pituitary
• Thyroid
• Parathyroid
• Adrenal
• Pancreas
• Ovaries
• Testes.



Classification of Hormones: hormones can be classified chemically into **three major groups:**

1. ***Steroid hormones:*** These are steroid in nature such as adrenocorticosteroid hormones, androgens, estrogens and progesterone.
2. ***Amino acid derivatives:*** These are derived from amino acid tyrosine, e.g. epinephrine, norepinephrine and thyroid hormones.
3. ***Peptide/Protein hormones:*** These are either large proteins or small or medium size peptides, e.g. Insulin, glucagon, parathormone, calcitonin, pituitary hormones, etc.

Several other glandular tissues are considered to secrete hormones, viz.:

• **Juxtaglomerular *(JG) cells of kidney:*** May produce the hormone ***erythropoietin*** which regulates erythrocyte maturation, erythropoiesis.

• ***Thymus:*** This produces a hormone that circulates from this organ to stem cells in lymphoid organ inducing them to become immunologically competent lymphocytes.

• ***Pineal gland:*** It produces a hormone that antagonises the secretion or effects of ACTH. It also produces factors called **glomerulotrophins** that regulates the adrenal secretion of aldosterone.

• ***GI tract:*** Few hormones are also produced by certain Specialised cells of GI tract and they are called GI Hormones.

Factors Regulating Hormone Action

Action of a hormone at a target organ is regulated by four factors:

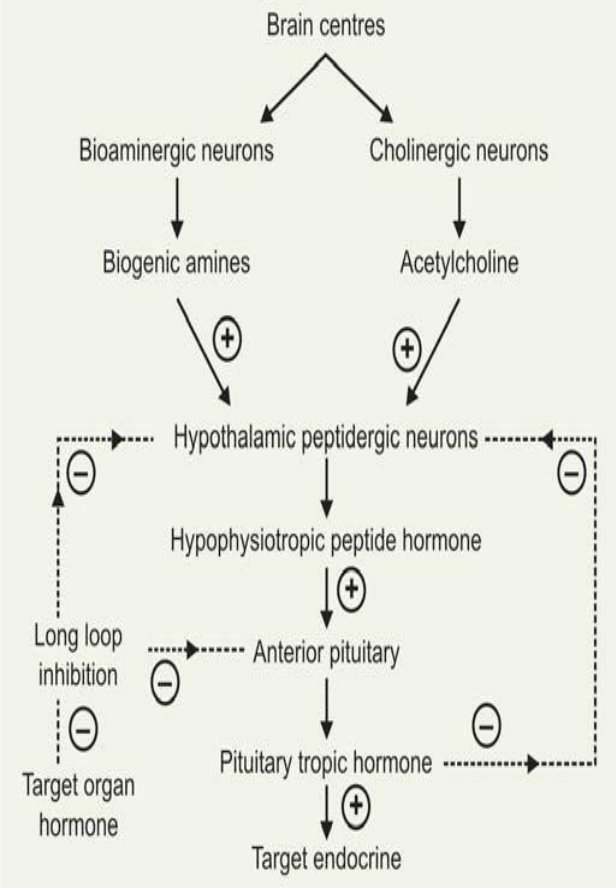
1. ***Rate of synthesis and secretion:*** The hormone is stored in the endocrine gland.
2. In some cases, ***specific transport systems in plasma.***
3. ***Hormone-specific receptors in target cell membranes*** which differ from tissue to tissue, and
4. ***Ultimate degradation*** of the hormone usually by the liver or kidneys.

REGULATION OF HORMONE SECRETION

Hormone secretion is strictly under control of several mechanisms.

A. Neuroendocrinal control mechanism: Nerve impulses control some endocrine secretions. Cholinergic sympathetic fibres stimulate catecholamine secretion from adrenal medulla. Centers in the midbrain, brainstem, hippocampus, etc. can send nerve impulses which react with the hypothalamus through cholinergic and bioaminergic neurons. At the terminations of these neurons, they release acetylcholine and biogenic amines to regulate the secretions of hypophysiotropic peptide hormones from hypothalamic peptidergic neurons. Some of the endocrine releases are controlled by either stimulatory or inhibitory hormones from a controlling gland, e.g. corticosteroids are controlled by corticotropin and thyroid hormones are controlled by thyrotropin from anterior pituitary. The tropins are further regulated by hypothalamic releasing hormones.

B. Feedback control mechanism: It is due mainly to negative feedback that such control is brought about. When there is a high blood level of a target gland hormones, it may inhibit the secretion of the tropic hormone stimulating that gland. Adrenal cortex secretes a hormone called cortisol which bring about the inhibition of secretion of corticotropin from anterior pituitary and corticotropin releasing hormone from the hypothalamus by long-loop feedback. This leads to reduction in cortisol secretion.



C. Endocrine rhythms: There are certain cyclic rhythms associated with the secretion of hormones over a period of time. When there is a cyclic periodicity of 24 hours, it is called as ***circadian rhythm***. However, if it is more than 24 hours, it is named as ***infradian rhythm*** and when it is less than 24 hours it is called as ***ultradian rhythm***. Due to such rhythms, the highest and lowest conc. of corticotropin is normally found in the morning and around midnight. Growth hormone and prolactin rise in the early hours of deep sleep. ***Cortisol peak is found between 4 AM and 8 AM. Endocrine rhythms result from cyclic activities of a biological clock in the limbic system, supplemented by the diurnal light-dark and sleep activity cycles and mediated by the hypothalamus***

Posttest

الاختبار البعدي:

Write the Dissimilarities of Hormone and Enzyme

References:

المصادر:

Textbook of Medical Biochemistry Eighth Edition 2012. MN Chatterjea Rana Shinde

الجامعة التقنية الوسطى
كلية التقنيات الصحية والطبية بغداد
قسم المختبرات الطبية/ المرحلة/ الثالثة
المادة: علم الغدد الصماء السريرية(Clinical Endocrinology)

Title: **العنوان:**

L 2&3 (MECHANISM OF ACTION OF HORMONES)

Name of the instructor: **اسم المحاضر:**

Assist.prof.Dr. Huda Farhan Ahmed
Assist.prof.Dr. Ahmed Saadi Hassan

Target population: **الفئة المستهدفة:**

Students of the third stage of medical laboratories

Introduction: المقدمة:

Although the physiological apparently secondary effects of most of the hormones have been rather completely known for a number of years, their primary biochemical mechanisms of actions at a cellular/molecular level are also known in much details now. Many hormones serve as inducers or repressors in the genetically controlled synthesis of certain key cellular enzymes.

Pretest: الاختبار القبلي:

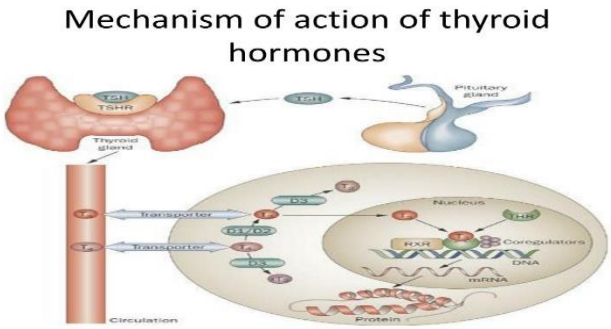
How do hormones actions?

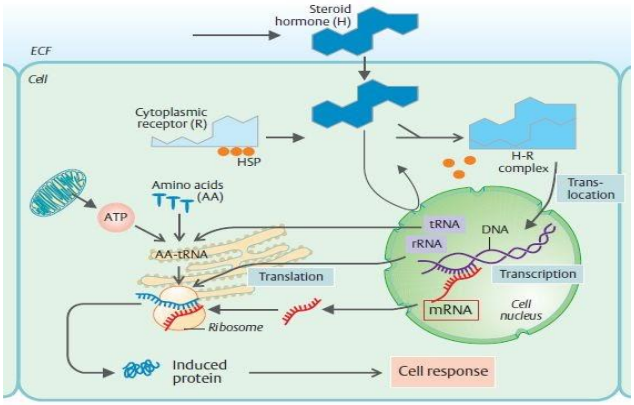
Scientific Content: المحتوى العلمي:

Although the physiological apparently secondary effects of most of the hormones have been rather completely known for a number of years, their primary biochemical mechanisms of actions at a cellular/molecular level are also known in much details now. Many hormones serve as inducers or repressors in the genetically controlled synthesis of certain key cellular enzymes.

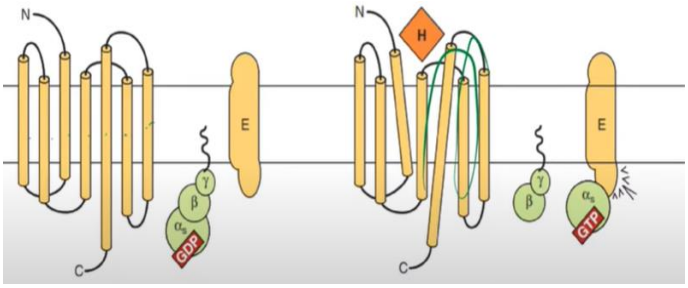
Protein (Enzymes or Channels) Synthesis	Protein (Enzymes or Channels) Activation
Genomic action. Lipid soluble hormones i.e., steroid, T3, T4.	Non-genomic action. Lipid insoluble hormones i.e., protein, peptide hormone, catecholamines, serotonin & melatonin.

1. Interaction with nuclear chromatin (nuclear action or genomic action):
Steroid hormones act mostly by changing the transcription rate of specific genes in the nuclear DNA. The steroid hormone has a specific soluble, oligomeric receptor protein (mobile receptor) either in the cytosol and/or inside the nucleus. This brings about conformational changes and also changes in the surface charge of the receptor protein to favour its binding to the nuclear chromatin attached to nuclear matrix. The ***receptor-steroid complex*** is translocated to the nuclear chromatin and binds to a steroid-recognising acceptor site called the ***hormone-responsive element (HRE)*** of a DNA strand on the upstream side of the promoter site for a specific steroid responsive gene. The consequent change in the intracellular concentration of m-RNA alters the rate of synthesis of a structural, enzymatic, carrier or receptor protein coded by it. This results in ultimate cellular effects. The receptor-steroid complex subsequently leaves the acceptor site as the free receptor and the steroid. In addition to regulating the transcription, some steroid hormones may also act as regulatory agents for post-transcriptional processing, stability and transport of specific mRNAs**.**

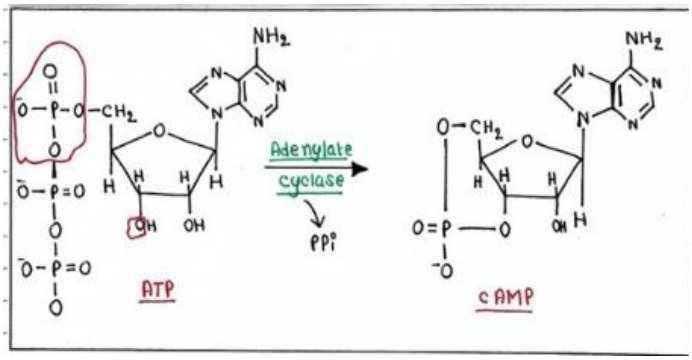




2. Membrane receptors (non-genomic action): certain molecules cannot enter target cells through the membrane lipid bilayer. This is achieved by the specific receptor molecules present on the surface of the plasma membrane. Many hormones seen specifically involved in the transport of a variety of substances across cell membrane. In general, these hormones specifically bind to the receptors on cell membrane. They cause rapid secondary metabolic changes in the tissue but have little effect on metabolic activity of membrane-free preparations. Most protein hormones and catecholamines activate transport of membrane enzyme systems by direct binding to specific receptors on the membrane.



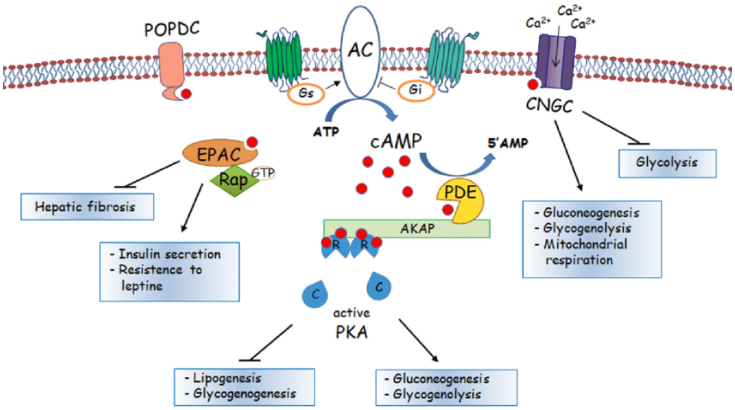
3. c-AMP and hormone action: ***3'-5' c-AMP plays a unique role in the action of many protein hormones***. Its level may be decreased or increased by hormonal action as the effect varies depending on the tissue. The hormones such as glucagon, catecholamines, PTH, etc. act by influencing a change in intracellular c-AMP concentration through the adenylate cyclase c-AMP system. The hormone binds to a specific membrane receptor.

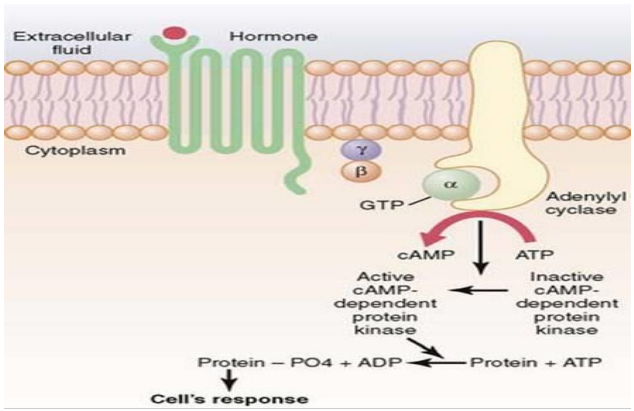


Different types of these receptors remain associated with either Gs or Gi type of GTP dependent trimeric nucleotide regulatory complexes of the membrane. Both Gs and Gi are made up of 3 subunits: Gs contains αs βγ while Gi contains αi βγ. Formation of the receptor-hormone complex promotes the binding of GTP to the α subunit of either Gs or Gi. When αs-GTP is released, it binds to adenylate cyclase located on the cytoplasmic surface of the membrane and changes its conformation to activate it. ***Adenylate cyclase*** catalyses the conversion of ATP to c-AMP thus increasing the intracellular concentration of the latter**.**

On the other hand, αi-GTP inhibits ***adenylate cyclase*** by binding with it. This lowers the intracellular concentration of c-AMP.

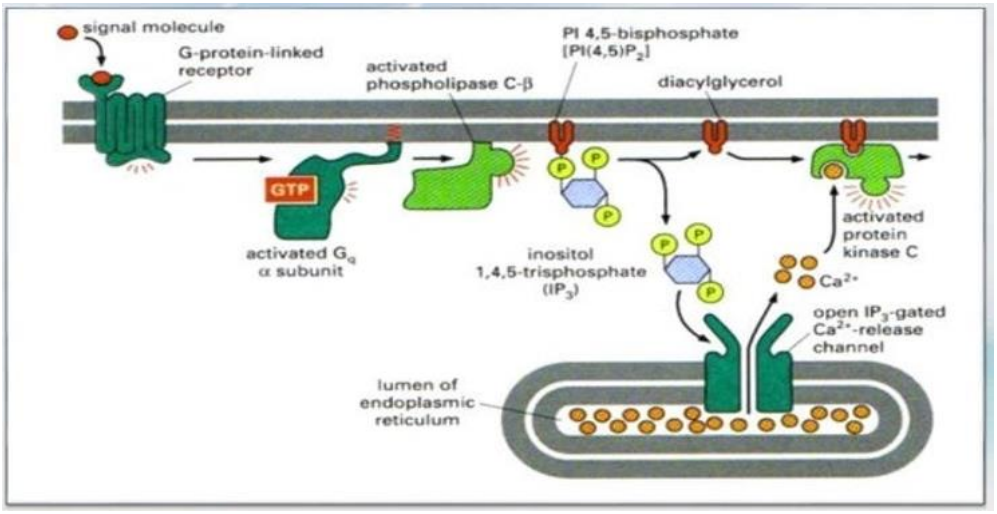
Note: Insulin can decrease hepatic c-AMP in opposition to the increase caused by glucagon.





4. Role of polyphosphoinositol and diacylglycerol in hormone action: Just like c-AMP other compounds such as 1, 4, 5 inositol triphosphate (ITP) and diacylglycerol (DAG) act as second messengers. This is specially found in case of vasopressin, TRH, GnRH, etc. These hormones activate the phospholipase C-polyphosphoinositol system to produce ITP and DAG. By binding with the specific receptor protein on cell membrane, the hormone activates a trimeric nucleotide regulatory complex. The complex in turn activates phospholipase C on the inner surface of the membrane. Inositol triphosphate enhances the mobilisation of Ca^{++} into the cytosol from intracellular Ca^{++} pool from mitochondria, calcium ions then act as tertiary messenger. While DAG activates the Ca^{++} phosphatidyl-serine-dependent

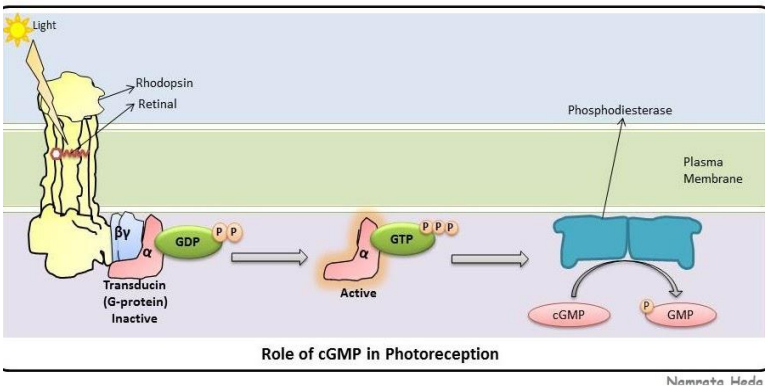
protein kinase C located on the inner surface of the membrane, by lowering its Km for Ca^{++}. This enzyme then phosphorylates specific enzymes and other proteins in the cytosol to modulate their activities.



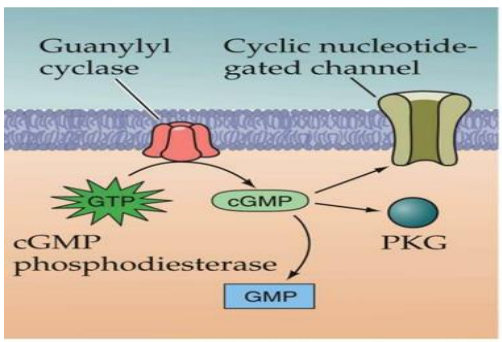
5. Role of calcium in hormone action: The action of most protein hormones is inhibited in absence of calcium even though ability to increase or decrease c-AMP is comparatively unimpaired. ***Thus, calcium may be more terminal signal for hormone action than c-AMP.*** It is suggested that ionised calcium of the cytosol is the important signal. ***The source of this calcium may be extracellular fluid or it may arise from mobilisation of intracellular tissue bound calcium.***

As mentioned, membrane-receptor binding may be responsible for this. The hormone receptor binding may directly inhibit the Ca^{++}–ATPase. It may also directly open up voltage-independent Ca^{++} channels in the membrane to increase the diffusion of Ca^{++} into the cell down its inward concentration gradient resulting in increased cytosolic Ca^{++} concentration which then acts as a second messenger to affect cellular activities. The receptor-hormone complex may produce ITP which in turn can increase cytosolic Ca^{++} concentration by enhancing the mobilisation of Ca^{++} from mitochondrial and endoplasmic reticular pools. All these enzymes have special biochemical metabolic roles. Ca^{++} also changes membrane permeability. Many of its effects are mediated through its binding to Ca^{++}–dependent regulatory proteins like calmodulin and troponin. (For calmodulin—refer to chapter on Glycogen Metabolism).

6. Role of c-GMP in hormone action: Hormones such as insulin and growth hormone affect the ***guanylate cyclase*** c-GMP system. This will increase the intracellular conc. of c-GMP and activate c-GMP-dependent protein kinases. The active c-GMP-protein kinase would in turn bring about phosphorylation of specific cellular proteins to change their activities, leading to relaxation of smooth muscles, vasodilatation and other effects. It is likely that Ca^{++} may act as a second messenger to activate guanylate cyclase and thereby increasing the conc. of c-GMP inside the cell.

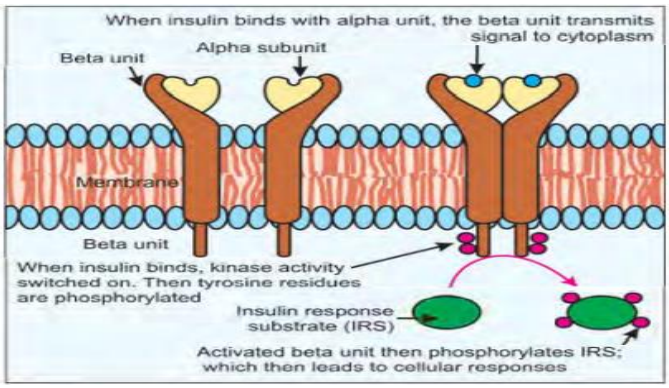


Role of cGMP in Photoreception



cGMP → PKG

7. Role of phosphorylation of tyrosine kinase: In fact, a second messenger for insulin, growth hormone, prolactin, oxytocin, etc. has not been identified so far. However, binding of them to their respective membrane receptors activates a specific protein kinase called ***tyrosine kinase*** which phosphorylates tyrosine residue of specific proteins. This may bring about some metabolic changes.



Hormone(s)	Origin	Major Function(s)
Group I. HORMONES THAT BIND TO INTRACELLULAR RECEPTORS		
Estrogens	Ovaries and adrenal cortex	Female sexual characteristics, menstrual cycle.
Progestins	Ovaries and placenta	Involved in menstrual cycle and maintenance of pregnancy.
Androgens	Testes and adrenal cortex	Male sexual characteristics, spermatogenesis.
Glucocorticoids	Adrenal cortex	Affect metabolisms, suppress immune system.
Mineralocorticoids	Adrenal cortex	Maintenance of salt and water balance.
Calcitriol (1, 25–DHCC)	Kidney (final form)	Promotes absorption of Ca^{2+} from intestine, kidney and bone.
Thyroid hormones (T_3, T_4)	Thyroid	Promote general metabolic rate.
Group II. HORMONES THAT BIND TO CELL SURFACE RECEPTORS		
A. The second messenger is cAMP		
Adrenocorticotropic hormone (ACTH)	Anterior pituitary	Stimulates the release of adrenocorticosteroids.
Follicle stimulating hormone (FSH)	Anterior pituitary	In females, stimulates ovulation and estrogen synthesis. In males, promotes spermatogenesis.
Luteinizing hormone (LH)	Anterior pituitary	Stimulates synthesis of estrogens and progesterone and causes ovulation. Promotes androgen synthesis by testes.
Chorionic gonadotropin (hCG)	Anterior pituitary	Stimulates progesterone release from placenta.
Thyroid stimulating hormone (TSH)	Anterior pituitary	Promotes the release of thyroid hormones (T_3, T_4).
β-Endorphins and enkephalins	Anterior pituitary	Natural endogenous analgesics (pain relievers).
Antidiuretic hormone (ADH)	Posterior pituitary (stored)	Promotes water reabsorption by kidneys.
Glucagon	Pancreas	Increases blood glucose level, stimulates glycogenolysis and lipolysis.
Parathyroid hormone (PTH)	Parathyroid	Increases serum calcium, promotes Ca^{2+} release from bone.
Calcitonin	Thyroid	Lowers serum calcium. Decreases Ca^{2+} uptake by bone and kidney.
Epinephrine	Adrenal medulla	Increases heart rate and blood pressure. Promotes glycogenolysis in liver and muscle and lipolysis in adipose tissue.
Norepinephrine	Adrenal medulla	Stimulates lipolysis in adipose tissue.
B. The second messenger is phosphatidyl inositol/calcium		
Thyrotropin-releasing hormone (TRH)	Hypothalamus	Promotes TSH release.
Gonadotropin-releasing hormone (GnRH)	Hypothalamus	Stimulates release of FSH and LH.
Gastrin	Stomach	Stimulates gastric HCl and pepsinogen secretion.
Cholecystokinin (CCK)	Intestine	Stimulates contraction of gall bladder and secretion of pancreatic enzymes.
C. The second messenger is unknown/unsettled		
Growth hormone (GH)	Anterior pituitary	Promotes growth of the body (bones and organs).
Prolactin (PRL)	Anterior pituitary	Growth of mammary glands and lactation.
Oxytocin	Posterior pituitary (stored)	Stimulates uterine contraction and milk ejection.
Insulin	Pancreas	Lowers blood glucose (hypoglycemic effect), promotes protein synthesis and lipogenesis.
Somatomedins (insulin-like growth factors, IGF-I, IGF-II)	Liver	Growth related functions of GH are mediated. Stimulates growth of cartilage.

Posttest

الاختبار البعدي:

Write about c-AMP and hormone action

References:

المصادر:

References: Textbook of Medical Biochemistry Eighth Edition 2012. MN Chatterjea Rana Shinde

الجامعة التقنية الوسطى
كلية التقنيات الصحية والطبية بغداد
قسم المختبرات الطبية/ المرحلة/ الثالثة
المادة: علم الغدد الصماء السريرية(Clinical Endocrinology)

Title: العنوان:

L4 (HYPOTHALAMUS HORMONES AND RELESING FACTORES)

Name of the instructor: اسم المحاضر:

Assist.prof.Dr. Huda Farhan Ahmed
Assist.prof.Dr. Ahmed Saadi Hassan

Target population: الفئة المستهدفة:

Students of the third stage of medical laboratories

Introduction: المقدمة:

The hypothalamus produces two types of endocrine factors;
(a) the hypothalamic neuropeptides
(b) the hypothalamic releasing factors. The releasing factors are inhibitory neuro-secretions synthesized in the hypothalamus and released through the hypothalamic pituitary portal circulation. They have their effect on the secretion of pituitary tropic hormones.

Pretest: الاختبار القبلي:

What is the hypothalamus?

Scientific Content: المحتوى العلمي:

The hypothalamus produces two types of endocrine factors;
(a) the hypothalamic neuropeptides
(b) the hypothalamic releasing factors. The releasing factors are inhibitory neuro-secretions synthesized in the hypothalamus and released through the hypothalamic pituitary portal circulation. They have their effect on the secretion of pituitary tropic hormones.

1. HYPOTHALAMIC NEUROPEPTIDES

The hypothalamic neuropeptides are produced by the supraoptic and paraventricular nuclei of the hypothalamus. These neurohormones are ***anti-diuretic hormone (ADH) and oxytocin***. The precursors of ADH and oxytocin are long polypeptides. They are synthesized in hypothalamus.

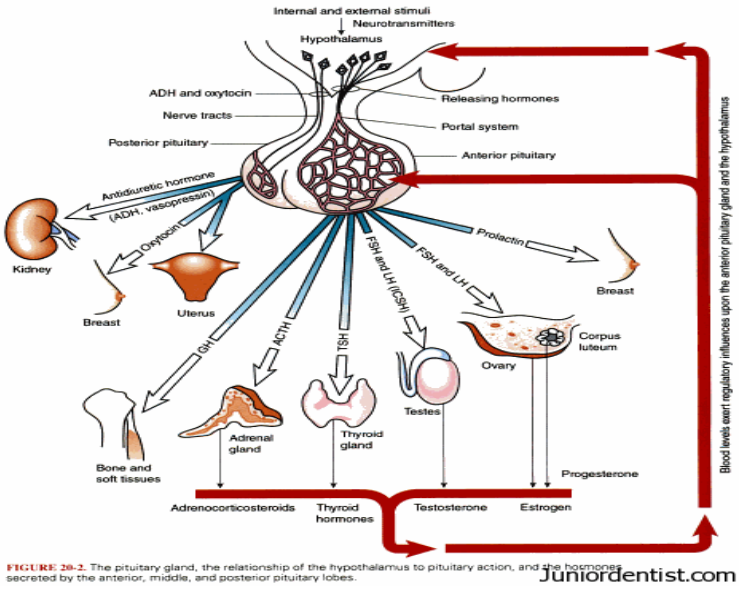


FIGURE 20-2. The pituitary gland, the relationship of the hypothalamus to pituitary action, and the hormones secreted by the anterior, middle, and posterior pituitary lobes.

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2. HYPOTHALAMIC RELEASING FACTORS

The secretion of hormones by adenohypophysis or anterior pituitary is under the control of peptides secreted by hypothalamus. Several peptides having effects on anterior pituitary, either stimulant (releasing factors), or inhibitory, have been identified. The secretion of the hypothalamic peptides is also under the feedback control of anterior pituitary tropic hormones (short loop feedback) as well as the target gland hormones.

The median eminence of the hypothalamus is connected directly to the pituitary stalk. Within this stalk is a portal system of blood vessels required to maintain normal secretory activity of the pituitary gland. The activities of the cells of the anterior lobe are controlled by the nerve cells of the hypothalamus which send axons to the capillary beds. The nerve endings liberate chemical substances, hypothalamic releasing factors or hormones. At present **10 discrete regulatory factors** have been described that may affect the synthesis as well as secretion of specific pituitary hormone.

Four hypothalamic- releasing hormones (GHRH, corticotropin- releasing hormone [CRH], thyrotropin-releasing hormone [TRH], and gonadotropin-releasing hormone [GnRH]) traverse the hypothalamic portal vessels and impinge upon their respective transmembrane trophic hormone-secreting cell receptors. These distinct cells express GH, ACTH, TSH, and gonadotropins, respectively. In contrast, hypothalamic somatostatin and dopamine suppress GH or PRL and TSH secretion, respectively.

Name	Chemical nature	Biological actions
TRH; thyrotropin releasing hormone	Tripeptide; (pyro-Glu-His-Pro-NH_2)	Induces secretion of TSH and PRL; neuromodulator
GnRH; gonadotropin releasing hormone	Biologically active portion is a decapeptide	Releases LH and FSH; induces spermatogenesis, ovulation and testosterone
GHRH; growth hormone releasing hormone	37-44 amino acid; amino terminal end is tyrosine	Stimulates growth hormone secretion
CRF; corticotropin releasing factor	Amidated peptide with 41 amino acids	Release of ACTH. Inhibited by cortisol.
Somatostatin; growth hormone inhibitory factor	Cyclic peptide with 14 amino acids	Inhibits secretion of GH and TSH. Inhibits gut hormones, pancreatic and gastric secretion
PIF; prolactin inhibitory factor	Dopamine	Inhibits PRL release

3. HORMONES OF ANTERIOR PITUITARY

The anterior pituitary hormones are tropic in nature, stimulating the secretion of hormones from target organs. Secretions of all these hormones are under the control of hypothalamic releasing or inhibitory factors.

REGULATION OF HORMONE SECRETION

Hormone secretion is strictly under control of several mechanisms.

A. Neuroendocrinal control mechanism: Nerve impulses control some endocrine secretions. Cholinergic sympathetic fibres stimulate catecholamine secretion from adrenal medulla. Centres in the midbrain, brainstem, hippocampus, etc. can send nerve impulses which react with the hypothalamus through cholinergic and bioaminergic neurons. At the terminations of these neurons, they release acetylcholine and biogenic amines to regulate the secretions of hypophysiotropic peptide hormones from hypothalamic peptidergic neurons. Some of the endocrine releases are controlled by either stimulatory or inhibitory hormones from a controlling gland, e.g. corticosteroids are controlled by corticotropin and thyroid hormones are controlled by thyrotropin from anterior pituitary. The tropins are further regulated by hypothalamic releasing hormones**.**

B. Feedback control mechanism: It is due mainly to negative feedback that such control is brought about. When there is a high blood level of a target gland hormones, it may inhibit the secretion of the tropic hormone stimulating that gland. Adrenal cortex secretes a hormone called cortisol which bring about the inhibition of secretion of corticotropin from anterior pituitary and corticotropin releasing hormone from the hypothalamus by long-loop feedback. This leads to reduction in cortisol secretion.

C. Endocrine rhythms: There are certain cyclic rhythms associated with the secretion of hormones over a period of time. When there is a cyclic periodicity of 24 hours, it is called as ***circadian rhythm.*** However, if it is more than 24 hours, it is named as ***infradian rhythm*** and when it is less than 24 hours it is called as ***ultradian rhythm*****.** Due to such rhythms, the highest and lowest conc. of corticotropin is

normally found in the morning and around midnight. Growth hormone and prolactin rise in the early hours of deep sleep. ***Cortisol peak is found between 4 AM and 8 AM. Endocrine rhythms result from cyclic activities of a biological clock in the limbic system, supplemented by the diurnal light-dark and sleep activity cycles and mediated by the hypothalamus.***

Posttest الاختبار البعدي:

Explain the regulation of hormone secretion

References: المصادر:

1-BIOCHEMISTRY (Dr. U. Satyanarayana Dr. U. Chakrapani) M.Sc., Ph.D., F.I.C., F.A.C.B. *Professor of Biochemistry & Director (Research)*/Fourth Revised Edition: 2013/ISBN: 978-81-312-3601-7

2-TEXTBOOK OF BIOCHEMISTRY Sixth Edition For Medical Students. © 2011, DM Vasudevan, Sreekumari S, Kannan Vaidyanathan

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كلية التقنيات الصحية والطبية بغداد
قسم المختبرات الطبية/ المرحلة/ الثالثة
المادة: علم الغدد الصماء السريرية(Clinical Endocrinology)

Title: **العنوان:**

L5 (PITUTARY ANTERIOR GLAND)

Name of the instructor: **اسم المحاضر:**

Assist.prof.Dr. Huda Farhan Ahmed
Assist.prof.Dr. Ahmed Saadi Hassan

Target population: **الفئة المستهدفة:**

Students of the third stage of medical laboratories

Introduction: المقدمة:

The hormones secreted by the anterior lobe of the pituitary gland are:

- **Growth hormone**
- **Pituitary tropic hormones** such as prolactin, gonadotropins FSH and LH, Thyrotropic hormones (TSH) and Adrenocorticotropic Hormone (ACTH).

Pretest: الاختبار القبلي:

What hormones are secreted by the anterior pituitary gland?

Scientific Content: المحتوى العلمي:

The hormones secreted by the anterior lobe of the pituitary gland are:

• ***Growth hormone***
• ***Pituitary tropic hormones*** such as **prolactin**, gonadotropins **FSH and LH**, Thyrotropic hormones **(TSH)** and Adrenocorticotropic Hormone **(ACTH).**

GROWTH HORMONE (SOMATOTROPIN)

The growth hormone (or somatotropin) is produced by somatotropin, a special group of acidophilic cells of anterior pituitary.

Regulation of GH release: Two hypothalamic factors play a prominent role in the release of growth hormones. These are the growth hormone releasing hormone (GRH) that stimulates and the growth hormone release-inhibiting hormone (GRIH, somatostatin) that inhibits. This, in turn, is regulated by a feedback mechanism.

Growth hormone production is influenced by many factors such as sleep, stress (pain, cold, surgery), exercise, food intake etc. It is observed that the largest increase in the production of GH occurs after the onset of sleep. This supports the adage "If you don't sleep, you won't grow."

Biochemical functions of GH: Growth hormone promotes growth, and also influences the normal metabolisms (protein, carbohydrate, lipid and mineral) in the body.

1. **Effects on growth:** As is obvious from the name, GH is essential for the growth. The growth-related effects of GH are mediated through insulin like growth factor I (IGF-I) which is also known as **somatomedin C** (formerly sulfation factor), produced by liver.
2. **Effects on protein metabolism:** Growth hormone has an anabolic effect on protein metabolism. It promotes the uptake of amino acids into the tissues and increases the protein synthesis. The overall effect of GH is a positive nitrogen balance that leads to increase in body weight.
3. **Effects on carbohydrate metabolism:** Growth hormone is antagonistic to insulin and causes hyperglycemia. GH increases gluconeogenesis, decreases glucose utilization, impairs glycolysis and reduces the tissue uptake of glucose.
4. **Effects on lipid metabolism:** Growth hormone promotes lipolysis in the adipose tissue and increases the circulatory levels of free fatty acids and their oxidation. It increases ketogenesis, particularly in diabetes.
5. **Effects on mineral metabolism:** Growth hormone promotes bone mineralization and its growth, as clearly observed in the growing children.

Abnormalities of GH production

Deficiency of GH: Impairment in the secretion of growth hormone in the growing age causes **dwarfism**. The other deficiency metabolic effects are not that serious in nature.

Overproduction of GH: Excessive production of GH causes **gigantism in children** and **acromegaly in adults**. This usually occurs in the acidophil tumor of pituitary gland. Gigantism is characterized by increased growth of long bones and this is observed before the epiphyseal plates close. Acromegaly occurs after epiphyseal closure and is characterized by increase in the size of hands, facial changes (enlarged nose, protruding jaw), excessive hair, thickening of skin etc.

PITUITARY TROPIC HORMONES

In addition to GH, anterior pituitary gland secretes some tropic hormones usually called as pituitary tropins.

What are "tropins"?

A tropin or tropic hormone is the one which influences the activities of other endocrine gland, principally those involved in stress and reproduction. These are carried by the blood to another target gland. The pituitary tropins are under the positive and negative control of peptide factors from hypothalamus. Further the tropic hormones are usually subject to feedback inhibition at the pituitary or hypothalamic level by hormone product of the final target gland. Prolactin (mammotropin), TSH (or thyrotropin), FSH and LH (gonadotropins), ACTH (corticotropin) are the tropic hormones secreted by the pituitary gland.

A. Prolactin: PRL or Leuteotropic Hormone (LTH)

It is ***secreted by*** lactotroph **α-cells** of anterior pituitary and as already mentioned has sequence homology with growth hormone.

Metabolic role

• The main function of PRL is ***to stimulate mammary growth and the secretion of milk.*** By acting through specific glycoprotein receptors on plasma membrane of mammary gland cells, it stimulates mRNA synthesis. This ultimately leads to enlargement of breasts during pregnancy. This is called as ***mammotropic action*****.**

• The synthesis of milk proteins such as lactalbumin, and casein takes place after parturition such an effect is called as ***lactogenic action.***

• Estrogens, thyroid hormones and glucocorticoids increase the number of prolactin receptors on the mammary cell membrane.

• Progesterone has the opposite effect.

B. Thyrotropic Hormone or Thyroid Stimulating Hormone (TSH)

This is ***produced by basophil cells*** of anterior pituitary and is ***glycoprotein*** in nature. This ***consists of α and β subunits.***

Note: The α*-subunit of TSH, LH, HCG and FSH are nearly identical.*

Metabolic role

There are receptors on the thyroid cell membrane which bind to the receptor binding site on β-subunit of TSH. The complex then activates ***adenylate cyclase*** which catalyses the formation of c-AMP which acts as the second messenger for most TSH actions as follows:

• ***The TSH stimulates the synthesis of thyroid hormones at all stages*** such as Iodine uptake, organification and coupling.

• It enhances the release of stored thyroid hormones.

• It increases DNA content, RNA and translation of proteins, cell size.

• It stimulates glycolysis, TCA cycle, HMP and phospholipid synthesis. Stimulation of last two does not involve c-AMP.

• It activates adipose tissue ***lipase*** to enhance the release of fatty acids (lipolysis).

C. Adrenocorticotropic Hormone (ACTH) or Corticotropin. **Two forms** have been isolated, ***α-corticotropin*** and **β*-corticotropin.***

ACTH is ***synthesised as a part of precursor peptide.*** The precursor molecule is synthesised as a glycoprotein called **Pro-opiomelanocortin peptide (POMC)**. Various proteolytic enzyme hydrolyses POMC to give different peptides. ***Thus, POMC is broken down into ACTH, β-lipotropin (LPH). β-LPH is further cleaved into γ-LPH and endorphins.***

Metabolic role

• The principal actions of corticotropin are exerted on the adrenal cortex and extraadrenal tissue. ***ACTH increases the synthesis of corticosteroids by the adrenal cortex and also stimulates their release from***

the gland. Profound changes in the adrenal structure, chemical composition and enzymatic activity are observed as a response to ACTH. Total protein synthesis is found to be increased. Thus, ACTH produces both a tropic effect on steroid production and tropic effect on adrenal tissue. It is observed that ACTH has specific receptors on cells of fasciculata which increases c-AMP levels in the cell. This activation is calcium dependent. This results in DNA content and RNA is transcribed. This leads to proliferation of fasciculata cells and growth of adrenal cortex.

• ACTH also stimulates the synthesis and secretion of glucocorticoids.
• ACTH is found to increase the transfer of cholesterol from plasma lipoproteins into the fasciculata cells.
• The ACTH induces rise in c-AMP, brings about phosphorylation and activation of cholesterol esterase. The enzyme action ultimately makes a large pool of free cholesterol.
• Corticotropin promotes the binding of cholesterol to mitochondrial cytochrome P450 required for hydroxylating cholesterol.
• It activates the rate limiting enzyme for conversion of cholesterol to pregnenolone.
• It activates dehydrogenases of HMP to increase the conc. of NADPH required for hydroxylation.
• By activating *adenylate cyclase* of adipose tissue it increases intracellular c-AMP which in turn activates hormone sensitive lipase. This enzyme is involved in lipolysis which increases the level of free fatty acids.
• It leads to increased ketogenesis and decreased RQ.
• Direct effects on carbohydrate metabolism include:
• **Lowering of blood glucose ↓;**
• Increase in glucose tolerance;
• Deposition of glycogen in adipose tissue is increased, regarded as due to stimulation of insulin secretion.
• ***It has MSH activity*** due to homology in amino acid sequence.

D. Pituitary Gonadotropins

These tropic hormones influence the function and maturation of the testes and ovary and are of **two types:**

• ***Follicle Stimulating Hormone (FSH)***
• ***Luteinizing Hormone (LH)***

Both of them are glycoproteins with sialic acid. As already mentioned, FSH and LH are dimers of α and β-chains linked noncovalently. ***The α-chain is identical for TSH, FSH and LH of the same species.***

Metabolic Role of FSH

It brings about its action by specific receptor binding and c-AMP.

Role of FSH in Spermatogenesis

The conversion of primary spermatocytes into secondary spermatocytes in the seminiferous tubules is stimulated by FSH. ***In absence of FSH, spermatogenesis cannot proceed. However, FSH by itself cannot cause complete formation of spermatozoa. For its completion, testosterone is also required.*** Thus, FSH seems to initiate the proliferation process of spermatogenesis, and testosterone is apparently ***necessary for final maturation of spermatozoa.*** Since the testosterone is secreted under the influence of LH, ***both FSH and LH must be secreted for normal spermatogenesis.***

Metabolic Role of LH

This hormone is **also known as interstitial cells stimulating hormone (ICSH).**

Action of LH in Ovulation: Ovulatory surge for LH It is necessary for final follicular growth and ovulation. Without this hormone, even though large quantities of FSH are available, the follicle will not progress to the stage of ovulation. ***LH acts synergistically with FSH to cause rapid swelling of the follicle shortly before ovulation.*** It is worth noting that especially large amount of LH called ***ovulatory surge*** is secreted by the pituitary during the day immediately preceding ovulation.

Regulation of Testosterone Secretion by LH Testosterone is produced by the interstitial cells of Leydig only when the testes are stimulated by LH from the pituitary gland, and the quantity of testosterone secreted varies approximately in proportion to the amount of LH available. Thus, ***in males, LH stimulates the development and functional activity of Leydig cells (interstitial) and consequently testicular androgen.***

Posttest

الاختبار البعدي:

Define somatotropin and its role in metabolism

References:

المصادر:

1-BIOCHEMISTRY (Dr. U. Satyanarayana Dr. U. Chakrapani) M.Sc., Ph.D., F.I.C., F.A.C.B. *Professor of Biochemistry & Director (Research)*/Fourth Revised Edition: 2013/ISBN: 978-81-312-3601-7

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قسم المختبرات الطبية/ المرحلة/ الثالثة
المادة: علم الغدد الصماء السريرية(Clinical Endocrinology)

Title: **العنوان:**

L6 (MIDDLE LOBE OF PITUITARY AND POSTIERIOR PITIUTARY GLAND)

Name of the instructor: **اسم المحاضر:**

Assist.prof.Dr. Huda Farhan Ahmed
Assist.prof.Dr. Ahmed Saadi Hassan

Target population: **الفئة المستهدفة:**

Students of the third stage of medical laboratories

Introduction: المقدمة:

Melanocyte Stimulating Hormones: The hormones secreted by intermediate lobe or middle lobe of pituitary gland are called melanocyte-stimulating hormones or MSH. POMC is the precursor molecule which is cleaved by *proteases* to give ACTH and β-lipotropin. The ACTH is further cleaved to β-MSH which has 13 amino acids. There is also α-MSH which is present in larger quantities. Amino acids 11-17 of β-MSH are common to both α-MSH and ACTH. ***MSH darkens the skin and is involved in skin pigmentation by deposition of melanin by melanocytes.***

Pretest: الاختبار القبلي:

How many types of secretions of the posterior pituitary gland?

Scientific Content: المحتوى العلمي:

HORMONE OF MIDDLE LOBE OF PITUITARY

Melanocyte Stimulating Hormones: The hormones secreted by intermediate lobe or middle lobe of pituitary gland are called melanocyte-stimulating hormones or MSH. POMC is the precursor molecule which is cleaved by ***proteases*** to give ACTH and β-lipotropin. The ACTH is further cleaved to β-MSH which has 13 amino acids. There is also α-MSH which is present in larger quantities. Amino acids 11-17 of β-MSH are common to both α-MSH and ACTH. ***MSH darkens the skin and is involved in skin pigmentation by deposition of melanin by melanocytes.***

HORMONES OF POSTERIOR PITUITARY LOBE

The hormones have been isolated and characterised from extracts of posterior pituitary gland. They are:

1. ***Vasopressin (Pitressin) or Arginine Vasopressin (ADH)***

2. ***Oxytocin.***

Both are small peptides containing nine amino acids. Oxytocin differs from Vasopressin with respect to 3rd and 8th amino acid residues.

Posterior pituitary hormones are synthesised in neurosecretory neurons. They are ***stored in the pituitary in association with two proteins neurophysin I and II.*** The release of these two hormones is independent of each other.

A. Metabolic Role of Vasopressin

1. Antidiuretic action: Antidiuretic effect is its main function. It reabsorbs water from the kidneys by distal tubules and collecting ducts. It is found to be mediated through formation of c-AMP. It is released due to rise in plasma osmolarity. This leads to formation of hypertonic urine having low volume, high sp. gr. and high conc. Of Na^+, Cl^-, phosphate and urea.

2. Urea-retention effect: Permeability of medullary collecting ducts to urea is increased by vasopressin. This leads to retention of urea and subsequently contributes to hypertonicity of the medullary interstitium. Urea retention effect can be reversed by phloretin.

3. Pressor effect: It stimulates the contraction of smooth muscles and thus causes vasoconstriction by increasing cytosolic Ca^{+2} concentration.

4. Glycogenolytic effect: By increasing intracellular calcium concentration.

CLINICAL IMPORTANCE

Condition of diabetes insipidus is described due to failure in secretion or action of vasopressin. It is characterised by very high volumes of urine output, up to 20-30 litres per day with a low specific gravity and excessive thirst.

• In primary, central or neurohypophyseal diabetes insipidus, vasopressin secretion is poor.

• In nephrogenic diabetes insipidus, kidneys cannot respond to vasopressin due to renal damage.

Inappropriate vasopressin secretion is characterised by a persistently hypertonic urine, progressive renal loss of Na^+ with low plasma levels of Na^+, symptoms of water intoxication like drowsiness, irritability, nausea, vomiting, convulsions, stupor and coma. It could be due to pulmonary infection and ectopic ADH secretions from lung tumours.

B. Metabolic Role of Oxytocin

Contraction of smooth muscle is the primary function of oxytocin. There are basically two effects, one on mammary glands called as ***galactobolic effect*** and the other on uterus called as ***uterine effect***.

1. Galactobolic effect: This is released due to neuroendocrinal reflex such as suckling of nipples. By doing so it causes the contraction of myoepithelial cells around mammary aleveoli and ducts and the smooth muscles surrounding the mammary milk sinuses; estrogen increases the number of oxytocin receptors during pregnancy while progesterone decreases the same and also inhibits the secretion of oxytocin.

2. Uterine effect: It is found to be elevated at full term pregnancy. It causes contraction of uterine muscle for child-birth. Estrogens enhance while progesterone decreases oxytocin receptors as well as its secretion. Oxytocin is also secreted during coitus by the female uterus which promotes the aspiration of semen into the uterus. This is also augmented by rise in estrogen in the follicular phase of menstrual cycle.

Posttest الاختبار البعدي:

What is the most important metabolic role of oxytocin?

References: المصادر:

Textbook of Medical Biochemistry (MN Chatterjea and Rana Shinde) Eighth Edition: 2012
ISBN 978-93-5025-484-4

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كلية التقنيات الصحية والطبية بغداد
قسم المختبرات الطبية/ المرحلة/ الثالثة
المادة: علم الغدد الصماء السريرية(Clinical Endocrinology)

Title: **العنوان:**

L 7&8 (THYROID GLAND)

Name of the instructor: **اسم المحاضر:**

Assist.prof.Dr. Huda Farhan Ahmed
Assist.prof.Dr. Ahmed Saadi Hassan

Target population: **الفئة المستهدفة:**

Students of the third stage of medical laboratories

Introduction: المقدمة:

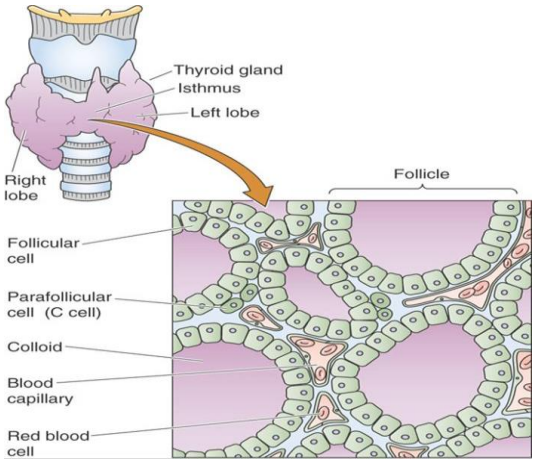
Thyroid gland (weighs about 30 g in adults) is located on either side of the trachea below the larynx. It produces, Thyroxine **(T_4), Tri-iodo thyronine (T_3)** and **'Reverse' T_3** by ***Follicular cells*** which regulate the metabolic rate of the body. Thyroid gland also secretes calcitonin by ***Parafollicular C-cells*** a hormone concerned with calcium homeostasis.

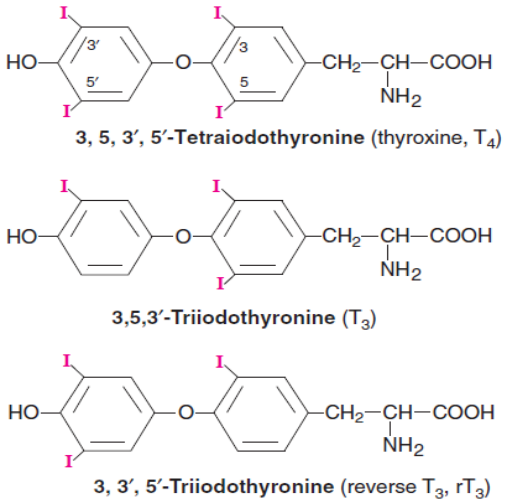
Pretest: الاختبار القبلي:

Where is the thyroid gland located?

Scientific Content: المحتوى العلمي:

Thyroid gland (weighs about 30 g in adults) is located on either side of the trachea below the larynx. It produces, Thyroxine **(T_4), Tri-iodo thyronine (T_3)** and **'Reverse' T_3** by ***Follicular cells*** which regulate the metabolic rate of the body. Thyroid gland also secretes calcitonin by ***Parafollicular C-cells*** a hormone concerned with calcium homeostasis.





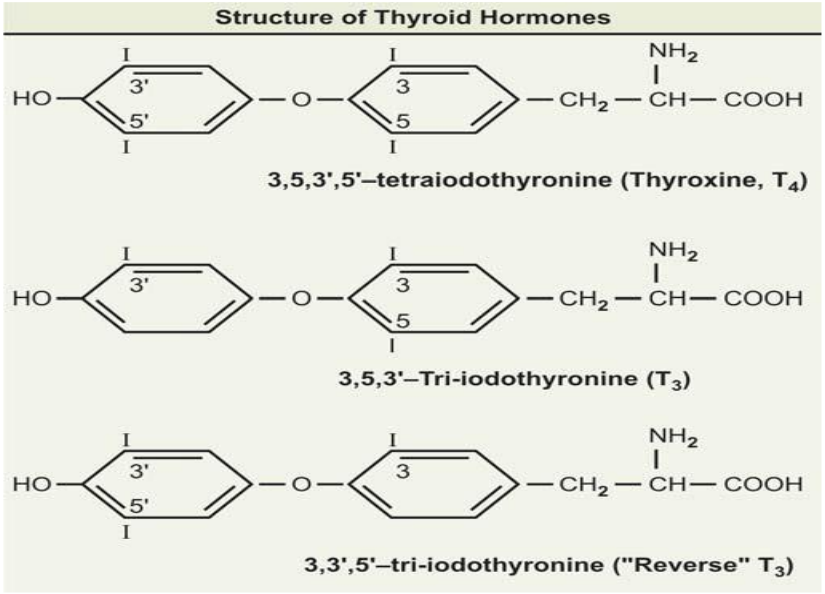
BIOSYNTHESIS OF THYROID HORMONES

Two raw materials (substrates) required by thyroid gland to synthesise the thyroid hormones are:

A. Thyroglobulin B. Iodine

A. Thyroglobulin and synthesis of T_3 and T_4: Thyroglobulin is a glycoprotein and precursor for the synthesis of T_3 and T_4. Thyroglobulin contains about 140 tyrosine residues which can serve as substrates for iodine for the formation of thyroid hormones.

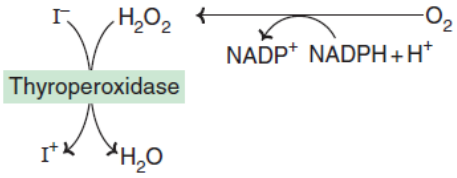
Tyrosine (of thyroglobulin) is first iodinated at position 3 to form monoiodotyrosine (MIT) and then at position 5 to form diiodotyrosine (DIT). Two molecules of DIT couple to form thyroxine (T_4). One molecule of MIT, when coupled with one molecule of DIT, triiodothyronine (T_3) is produced



B. Iodine

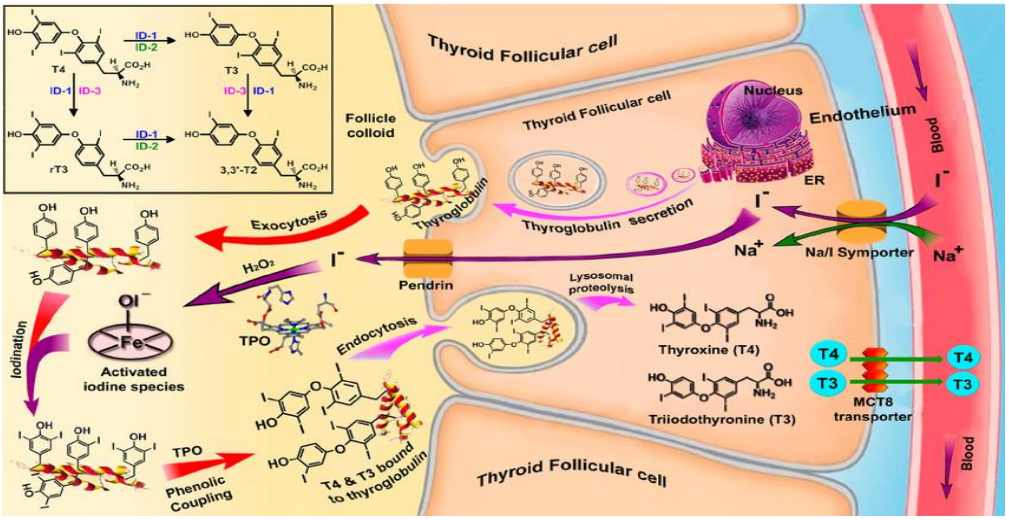
Uptake of iodide: The uptake of iodide by the thyroid gland occurs against a concentration gradient (about 20: 1). It is an energy requiring process and is linked to the ATPase dependent Na^+-K^+ pump. Iodide uptake is primarily controlled by TSH. Antithyroid agents such as thiocyanate and perchlorate inhibit iodide transport.

Formation of active iodine: The conversion of iodide (I^-) to active iodine (I^+) is an essential step for its incorporation into thyroid hormones. Thyroid is the only tissue that can oxidize I^- to a higher valence state I^+. This reaction requires H_2O_2 and is catalysed by the enzyme thyroperoxidase. An NADPH dependent system supplies H_2O_2.



Storage and release of thyroid hormones: Thyroglobulin containing **T_4** and **T_3** can be stored for several months in the thyroid gland. It is estimated that the stored thyroid hormones can meet the body requirement for 1-3 months. Thyroglobulin is digested by lysosomal proteolytic enzymes in the thyroid gland. The free hormones thyroxine (90%) and triiodothyronine (10%) is released into the blood, a process stimulated by TSH. MIT and DIT produced in the thyroid gland undergo deiodination by the enzyme deiodinase and the iodine thus liberated can be reutilized.

Transport of T_4 and T_3: Two specific binding proteins—thyroxine binding globulin (TBG) and thyroxine binding prealbumin (TBPA)—are responsible for the transport of thyroid hormones. Both T4 and T3 are more predominantly bound to TBG. A small fraction of free hormones is biologically active. T4 has a half-life of 4-7 days while T3 has about one day.



Biochemical functions of thyroid hormones

Triiodothyronine (**T_3**) is about four times **more active** in its biological functions **than** thyroxine (**T_4**). The following are the biochemical functions attributed to thyroid hormones (T_3 and T_4).

1. Influence on the metabolic rate: Thyroid hormones **stimulate the metabolic activities** and increases the oxygen consumption in most of the tissues of the body (exception—brain, lungs, testes and retina). **Na^+-K^+ ATP pump:** This is an energy dependent process which consumes a major share of cellular ATP. Na^+-K^+ ATPase activity is directly correlated to thyroid hormones and this, in turn, with ATP utilization.

Obesity in some individuals is attributed to a decreased energy utilization and heat production due to diminished Na^+-K^+ ATPase activity.

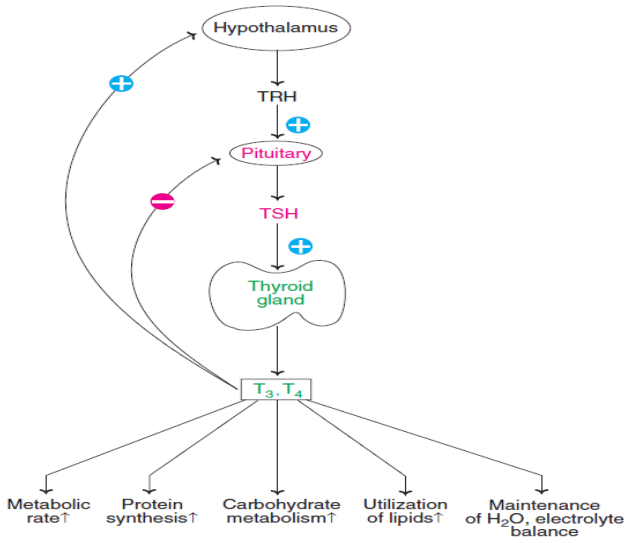
2. Effect on protein synthesis: Thyroid hormones act like steroid hormones in promoting protein synthesis by acting at the transcriptional level (activate DNA to produce RNA). Thyroid hormones, thus, function as anabolic hormones and cause positive nitrogen balance and promote growth and development.

3. Influence on carbohydrate metabolism: Thyroid hormones promote intestinal absorption of glucose and its utilization. These hormones increase gluconeogenesis and glycogenolysis, with an overall effect of enhancing blood glucose level (hyperglycemia).

4. Effect on lipid metabolism: Lipid turnover and utilization are stimulated by thyroid hormones. Hypothyroidism is associated with elevated plasma cholesterol levels which can be reversed by thyroid hormone administration.

Regulation of T3 and T4 synthesis

The synthesis of thyroid hormones is controlled by feedback regulation. T_3 appears to be more actively involved than T_4 in the regulation process. The production of thyroid stimulating hormone (TSH) by pituitary, and thyrotropin releasing hormone (TRH) by hypothalamus are inhibited by T_3 and, to a lesser degree, by T_4. The increased synthesis of TSH and TRH occurs in response to decreased circulatory levels of T_3 and T_4. As already discussed, the body has sufficient stores of hormones to last for several weeks. Hence it takes some months to observe thyroid functional deficiency.



Metabolic fate of T_3 and T_4

Thyroid hormones undergo deiodination in the peripheral tissues. The iodine liberated may be reutilized by the thyroid. T_3 and T_4 may get conjugated with glucuronic acid or sulfate in the liver and excreted through bile. Thyroid hormones are also subjected to deamination to produce tetraiodothyroacetic acid (from T_4) and triiodothyroacetic acid (from T_3) which may then undergo conjugation and excretion.

Abnormalities of thyroid function

Among the endocrine glands, **thyroid is the most susceptible for hypo- or hyperfunction**. Three abnormalities associated with thyroid functions are known.

Goiter: Any abnormal increase in the size of the thyroid gland is known as goiter. Enlargement of thyroid gland is mostly to compensate the decreased synthesis of thyroid hormones and is associated with **elevated TSH**. Goiter is primarily due to a failure in the autoregulation of T3 and T4 synthesis. This may be caused by deficiency or excess of iodide.

Goitrogenic substances (goitrogens): These are the substances that interfere with the production of thyroid hormones. These include thiocyanates, nitrates and perchlorates and the drugs such as thiourea, thiouracil, thiocarbamide etc. Certain plant foods—cabbage, cauliflower and turnip—contain goitrogenic factors (mostly thiocyanates).

Simple endemic goiter: This is due to iodine deficiency in the diet. It is mostly found in the geographical regions away from sea coast where the water and soil are low in iodine content. Consumption of iodized salt is advocated to overcome the problem of endemic goiter. In certain cases, administration of thyroid hormone is also employed.

Hyperthyroidism: This is also known as **thyrotoxicosis** and is associated with overproduction of thyroid hormones. Hyperthyroidism is characterized by increased metabolic rate (**higher BMR**) nervousness, irritability, anxiety, rapid heart rate, loss of weight despite increased appetite, weakness, diarrhea, sweating, sensitivity to heat and often protrusion of eyeballs (exophthalmos).
Hyperthyroidism is caused by **Grave's disease** (particularly in the developed countries) or due to increased intake of thyroid hormones. Grave's disease is due to elevated **thyroid stimulating IgG** also known as long-acting thyroid stimulator (LATS) which activates TSH and, thereby, increases thyroid hormonal production. Thyrotoxicosis is diagnosed by scanning and/or estimation of T3, T4 (both elevated) and TSH (decreased) in plasma. The treatment includes administration of antithyroid drugs. In severe cases, thyroid gland is surgically removed.

Hypothyroidism: This is due to an impairment in the function of thyroid gland that often causes decreased circulatory levels of T3 and T4. Disorders of pituitary or hypothalamus also contribute to hypothyroidism. Women are more susceptible than men. Hypothyroidism is characterized by **reduced BMR**, slow heart rate, weight gain, sluggish behavior, constipation, sensitivity to cold, dry skin etc.
Hypothyroidism in children is associated with physical and mental retardation, collectively known as **cretinism**. Early diagnosis and proper treatment are essential. Hypothyroidism in adult causes **myxoedema,** characterized by bagginess under the eyes, puffiness of face, slowness in physical and mental activities. Thyroid hormonal administration is employed to treat hypothyroidism.

Posttest الاختبار البعدي:

Discuss Grave's disease

References: المصادر:

1- BIOCHEMISTRY (Dr. U. Satyanarayana Dr. U. Chakrapani) M.Sc., Ph.D., F.I.C., F.A.C.B. *Professor of Biochemistry & Director (Research)*/Fourth Revised Edition: 2013/ISBN: 978-81-312-3601-7
2-Textbook of Medical Biochemistry Eighth Edition 2012. MN Chatterjea Rana Shinde

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قسم المختبرات الطبية/ المرحلة/ الثالثة
المادة: علم الغدد الصماء السريرية(Clinical Endocrinology)

Title: **العنوان:**

L9 (PARATHYROID GLAND)

Name of the instructor: **اسم المحاضر:**

Assist.prof.Dr. Huda Farhan Ahmed
Assist.prof.Dr. Ahmed Saadi Hassan

Target population: **الفئة المستهدفة:**

Students of the third stage of medical laboratories

Introduction: المقدمة:

PARATHORMONE (PTH): is essential for the physiologic actions of this hormone on both skeletal and renal tissues.

Pretest: الاختبار القبلي:

What is the importance of the parathyroid gland?

Scientific Content: المحتوى العلمي:

PARATHORMONE (PTH): is essential for the physiologic actions of this hormone on both skeletal and renal tissues.
Methionine is important amino acid and necessary for calcium mobilising effect.
Biosynthesis: PTH is initially synthesised in chief cells as a pro-hormone.
PTH thus formed is packaged and stored in secretory vesicles. Increased c-AMP concentration and a low Ca^{++} level stimulates its release from secretory vesicles. On the other hand, a high concentration of Ca^{++} stimulates the degradation of the stored PTH in secretory vesicles instead of its release.

METABOLIC ROLE OF PTH: The actions of PTH are reflected in the consequences of:
• ***Its administration***
• ***Removal of the parathyroid glands.***

A. *The most conspicuous metabolic consequences of administration of PTH are:*
• Increase in serum Ca^{++} concentration ↑.
• Decrease in serum inorganic PO4 ↓ concentration.
• Increased urinary Ca^{++} ↑ following an initial decrease.
• Increased urinary PO4 ↑.
• Removes Ca from bones, particularly if dietary intake of Ca is inadequate.
• Increase in 'citrate' ↑ content of blood plasma, kidney and bones.
• Activates vit D in renal tissue by increasing the rate of conversion of 25-OH-cholecalciferol to 1,25-di-OH-cholecalciferol, ***by stimulating α-1- hydroxylase enzyme.***
• ***Effect on Mg metabolism:*** PTH has been reported to exert an influence on Mg metabolism. Primary hyperparathyroidism has been found to be associated with excessive urinary excretion of Mg and –ve Mg balance.

B. Actions on Different Organs:
(a) Action on Kidneys:* PTH acts through by increasing c-AMP.** PTH binds to specific 'receptors' on plasma membrane of renal cortical cells of both proximal and distal tubules and stimulates ***adenyl cyclase to produce c-AMP ↑. c-AMP then is transported to apical/luminal part of the cell where it activates c-AMP dependent ***protein kinase,*** which phosphorylates specific proteins of the apical membrane to affect the several mineral transport, across the membrane.

• PTH decreases the transmembrane transport and reabsorption of filtered Pi in both proximal and distal tubular cells and increases the urinary excretion of inorganic phosphate ↑ ***(phosphaturic effect).***

• Fall in serum inorganic PO_4 level leads to mobilisation of PO_4 from bones, which also mobilises Ca^{++} along with, ***resulting to hypercalcaemia.***

• PTH ***stimulates α-1-hydroxylase*** enzyme located in mitochondria of proximal convoluted tubule cells, which converts 25-OHcholecalciferol, to 1-25, di-OH-cholecalciferol which in turn ***increases the intestinal and renal absorption of Ca^{++} resulting to hypercalcaemia.***

• PTH inhibits the transmembrane transport of K^+ and HCO_3^- to decrease their reabsorption by renal tubules.

• PTH increases the transmembrane transport and reabsorption of filtered Ca^{++} in the distal tubules resulting initially to decrease urinary excretion of Ca^{++}. But later on, PTH-induced hypercalcaemia enhances the amount of filtered Ca^{++} which increases the renal excretion.

(b) Action on Bones: PTH binds to specific 'receptors' present on membranes of osteoclasts, osteoblasts and osteocytes and increases cyclic AMP level in these cells, which acts through c-AMP dependent ***protein kinases*.**

Following actions are seen:

• ***Osteoclastic activity:*** It stimulates the differentiation and maturation of precursors cells of osteoclasts to mature osteoclasts.

• ***Osteoclastic osteolysis:*** PTH stimulates the osteoclasts through "second messenger" c-AMP to increase the resorption of bones which enhances mobilisation of Ca and P from bones.

• ***Osteocytic osteolysis:*** PTH also stimulates osteocytes which increases bone resorption thus mobilising Ca^{++} and Pi. There occurs enlargement of bone lacunae.

• ***Action on alkaline phosphatase:*** Alkaline phosphatase activity varies as per PTH concentration. At low concentrations, PTH stimulates the sulfation of cartilages and increases the number of osteoblasts and alkaline phosphatase activity of bone osteoblasts. At higher levels of physiological concentrations, PTH inhibits alkaline phosphatase activity and collagen synthesis in osteoblasts and decreases the Ca^{++} retaining capacity of bones. PTH induced rise in intracellular c-AMP in osteoclasts/and osteocytes leads to secretion of lysosomal hydrolases/and collagenases which increase breakdown of collagen and MPS in bones matrices.

(c) Action on Intestinal Mucosa: PTH does not act directly on intestinal mucosal cells as the cells do not possess the specific 'receptors' for PTH. But it increases the absorption of Ca^{++} and PO_4 through production, 1-25, di-OH-cholecalciferol (calcitriol).

Posttest: الاختبار البعدي:

Explain the role of PTH in calcium regulation

References: المصادر:

1- BIOCHEMISTRY (Dr. U. Satyanarayana Dr. U. Chakrapani) M.Sc., Ph.D., F.I.C., F.A.C.B. *Professor of Biochemistry & Director (Research)*/Fourth Revised Edition: 2013/ISBN: 978-81-312-3601-7

2- Textbook of Medical Biochemistry Eighth Edition 2012. MN Chatterjea Rana Shinde

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المادة: علم الغدد الصماء السريرية(Clinical Endocrinology)

Title: العنوان:

L10 (PANCREAS GLAND)

Name of the instructor: اسم المحاضر:

Assist.prof.Dr. Huda Farhan Ahmed
Assist.prof.Dr. Ahmed Saadi Hassan

Target population: الفئة المستهدفة:

Students of the third stage of medical laboratories

Introduction: المقدمة:

The hormone-secreting, endocrine portion of pancreas is the *islet of Langerhans*, which contains α**,** β**,** δ**,** and **F cells**. Insulin and glucagon are perhaps the most influential intermediary metabolism regulating hormones; insulin is released from the β-cells in response to high blood glucose levels (e.g. after a meal) and glucagon from α-cells in response to low blood glucose levels. ***The δ-cells produce somatostatin and F cells secrete pancreatic polypeptide***. All these pancreatic hormones are peptides and not under any major pituitary, hypothalamic, or neural control.

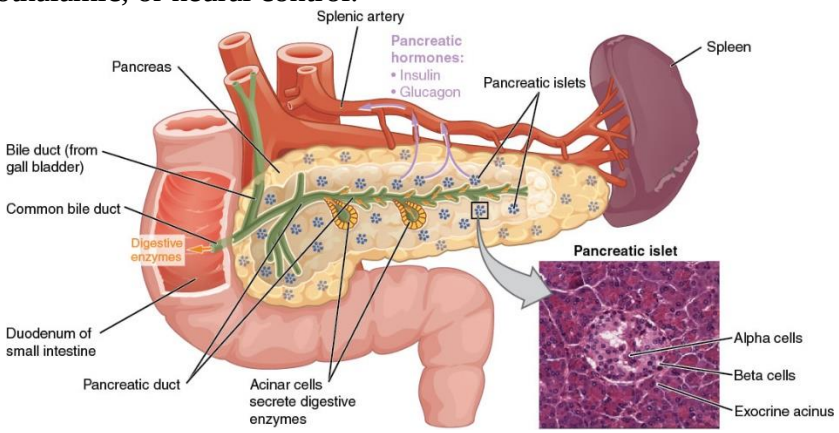
Pretest: الاختبار القبلي:

What is the most important hormone secreted by the pancreas?

Scientific Content: المحتوى العلمي:

Pancreatic Hormones

The hormone-secreting, endocrine portion of pancreas is the ***islet of Langerhans***, which contains α, β, δ, and **F cells**. Insulin and glucagon are perhaps the most influential intermediary metabolism regulating hormones; **insulin** is released from the **β-cells** in response to high blood glucose levels (e.g. after a meal) and **glucagon** from **α-cells** in response to low blood glucose levels. ***The δ-cells produce somatostatin and F cells secrete pancreatic polypeptide.*** All these pancreatic hormones are peptides and not under any major pituitary, hypothalamic, or neural control.



INSULIN

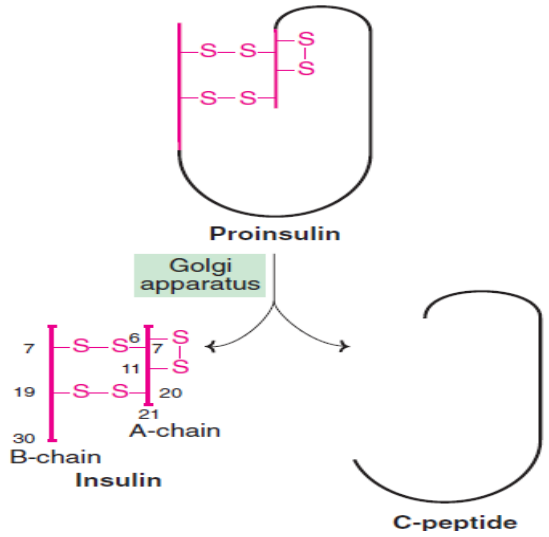
Insulin is ***a protein hormone***, secreted by β-cells of islets of Langerhans of pancreas. It plays an important role in metabolism causing increased carbohydrate metabolism, glycogenesis and glycogen storage; FA synthesis/TG storage and amino acid uptake/protein synthesis. **Thus, insulin is an important anabolic hormone** which act on variety of tissues. Major target tissues of insulin are the muscles, liver, adipose tissue and heart.

Note: RB cells, GI tract epithelial cells and renal tubular epithelial cells are rather generally unresponsive to insulin.

Chemistry: Insulin is a heterodimeric protein; has been isolated from pancreas and prepared in crystalline form. For crystallisation, it requires Zn^{++}. Zinc is also a constituent of stored insulin and normal pancreatic tissue is relatively rich in Zn. Insulin molecule is ***composed of two polypeptide chains, called 'A'-chain and 'B'-chain, containing total of 51 amino acids***. **A-chain** contains 21 amino acids and **B-chain** contains 30 amino acids. Both the chains are held together by two S–S linkages.

• ***Importance of S–S bridges:*** Breaking of the disulfide bonds with alkali or reducing agents inactivate insulin. Digestion of insulin protein with proteolytic enzymes also inactivates the hormone.

Note: ***The above is the reason why insulin cannot be given orally.***



Regulation of insulin secretion

About 40-50 units of insulin is secreted daily by human pancreas. The normal insulin concentration in plasma is 20-30 µU/ml. The important factors that influence the release of insulin from the β-cells of pancreas.

1. **Factors stimulating insulin secretion:** These include glucose, amino acids and gastrointestinal hormones.

2. **Factors inhibiting insulin secretion:** Epinephrine is the most potent inhibitor of insulin release. In emergency situations like stress, extreme exercise and trauma, the nervous system stimulates adrenal medulla to release epinephrine. **Epinephrine** suppresses insulin release and promotes energy metabolism by mobilizing energy-yielding compounds—glucose from liver and fatty acids from adipose tissue.

Degradation of insulin

In the plasma, insulin has a normal **half-life** of **4-5 minutes**. This short half-life permits rapid metabolic changes in accordance to the alterations in the circulating levels of insulin. This is advantageous for the therapeutic purposes. A protease enzyme, namely **insulinase** (mainly found in liver and kidney), degrades insulin.

Metabolic effects of insulin

Insulin plays a key role in the regulation of carbohydrate, lipid and protein metabolisms. Insulin exerts anabolic and anticatabolic influences on the body metabolism.

1. Effects on carbohydrate metabolism: In a normal individual, about half of the ingested glucose is utilized to meet the energy demands of the body (mainly through glycolysis). The other half is converted to fat (~ 40%) and glycogen (~ 10%). This relation is severely impaired in insulin deficiency. Insulin influences glucose metabolism in many ways. The net effect is that insulin **lowers blood glucose level (hypoglycemic effect)** by promoting its utilization and storage and by inhibiting its production.

*__Effect on glucose uptake by tissues: Insulin__ is **required** for the uptake of glucose **by muscle** (skeletal, cardiac and smooth), **adipose tissue**, leukocytes and mammary glands. Surprisingly, about 80% of glucose uptake in the body is not dependent on insulin. Tissues into which glucose can freely enter include brain, kidney, erythrocytes, retina, nerve, blood vessels and intestinal mucosa. As regards liver, glucose entry into hepatocytes does not require insulin. However, insulin stimulates glucose utilization in liver and, thus, indirectly promotes its uptake.

*__Effect on glucose utilization:__ Insulin **increases glycolysis** in muscle and liver. Glycogen production is enhanced by insulin by increasing the activity of glycogen synthetase.

*__Effect on glucose production:__ Insulin **decreases gluconeogenesis**

2. Effects on lipid metabolism: The net effect of insulin on lipid metabolism is to reduce the release of fatty acids from the stored fat and decrease the production of ketone bodies. Among the tissues, adipose tissue is the most sensitive to the action of insulin.

* **Effect on lipogenesis:** Insulin **favours** the **synthesis of triacylglycerols** from glucose

* **Effect on lipolysis:** Insulin decreases the activity of hormone-sensitive lipase and thus reduces the release of fatty acids from stored fat in adipose tissue.

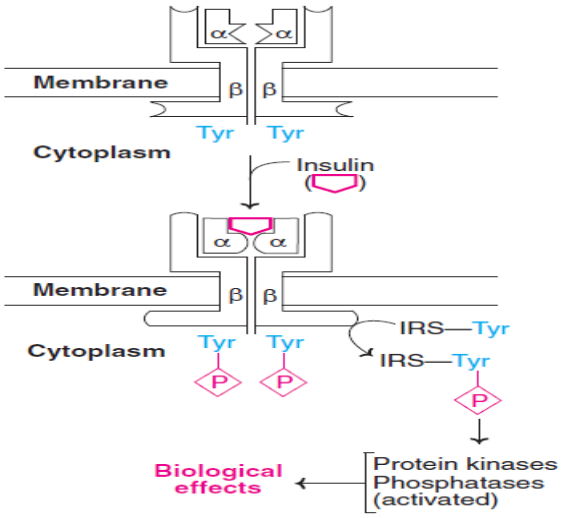
* **Effect on ketogenesis:** Insulin **reduces ketogenesis** by decreasing the activity of HMG CoA synthetase.

3. **Effects on protein metabolism:** Insulin is an anabolic hormone. It stimulates the entry of amino acids into the cells, **enhances protein synthesis** and reduces protein degradation.

Besides the metabolic effects described above, ***insulin promotes cell growth and replication***.

Mechanism of action of insulin

It is now recognized that **insulin binds to** specific plasma **membrane receptors** present on the target tissues, such as muscle and adipose. This results in a series of reactions ultimately leading to the biological action. Three distinct mechanisms of insulin action are known. One concerned with the induction of transmembrane signals (signal transduction), second with the glucose transport across the membrane and the third with induction of enzyme synthesis.



HYPOGLYCEMIA

When the blood glucose concentration falls to **less than 45 mg/dl**, the symptoms of hypoglycemia appear. The manifestations include headache, anxiety, confusion, sweating, slurred speech, seizures and coma, and, if not corrected, death. All these symptoms are directly and indirectly related to the deprivation of glucose supply to the central nervous system (particularly the brain) due to a fall in blood glucose level. The mammalian body has developed a well-regulated system for an efficient maintenance of blood glucose concentration (details already described). Hypoglycemia, therefore, is not commonly observed. The following three types of hypoglycemia are encountered by physicians.

1. **Post-prandial hypoglycemia**
2. **Fasting hypoglycemia**
3. **Hypoglycemia due to alcohol intake**
4. **Hypoglycemia due to insulin overdose**
5. **Hypoglycemia in premature infants**

CLASSIFICATION OF DIABETES MELLITUS

Diabetes mellitus is a **metabolic disease**, more appropriately a disorder of fuel metabolism. It is mainly characterized by **hyperglycemia** that leads to several long term complications. Diabetes mellitus is broadly divided into 2 groups, namely insulin-dependent diabetes mellitus (IDDM) and non-insulin dependent diabetes mellitus (NIDDM). This classification is mainly based on the requirement of insulin for treatment.

GLUCAGON

Glucagon, **secreted by α-cells** of the pancreas, opposes the actions of insulin. It is a polypeptide hormone composed of 29 amino acids in a single chain. Glucagon is actually synthesized as proglucagon which on sequential degradation releases active glucagon. Glucagon has a short half-life in plasma i.e. about 5 minutes.

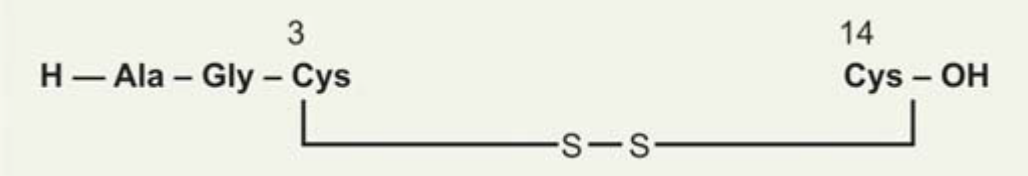
Regulation of glucagon secretion
The secretion of glucagon is **stimulated by low blood glucose** concentration, amino acids derived from dietary protein and low levels of epinephrine. Increased blood glucose level markedly inhibits glucagon secretion.

Metabolic effects of glucagon
Glucagon influences carbohydrate, lipid and protein metabolisms. In general, the effects of this hormone **oppose that of insulin**.
1. **Effects on carbohydrate metabolism:** Glucagon is the most potent hormone that enhances the blood glucose level (hyperglycemic). Primarily, glucagon acts on liver to cause increased synthesis of glucose (gluconeogenesis) and enhanced degradation of glycogen (glycogenolysis). The actions of glucagon are mediated through cyclic AMP.
2. **Effects on lipid metabolism:** Glucagon promotes fatty acid oxidation resulting in energy production and ketone body synthesis (ketogenesis).
3. **Effects on protein metabolism:** Glucagon increases the amino acid uptake by liver which, in turn, promotes gluconeogenesis. Thus, glucagon lowers plasma amino acids.

Mechanism of action of glucagon
Glucagon binds to the specific receptors on the plasma membrane and acts through the mediation of cyclic AMP, the second messenger.

SOMATOSTATIN

The peptide somatostatin (also called as **"GH release inhibiting factor"**) was first isolated from the hypothalamus and was implicated as a regulator of GH secretion.
Chemistry: It is a peptide consisting of 14 amino acids. There is an intrachain S–S linkage joining cysteine 3 and cysteine at position 14.



Source: There are ***three sources:***
1. ***Hypothalamus*** as stated above.
2. ***Pancreas:*** Somatostatin is also ***secreted by*** δ***-cells of islet of Langerhans of pancreas.***
3. ***GI tract:*** It is also ***produced by D-cells of antral mucosa of stomach*** and ***also duodenal mucosa.***
The above suggest that the hypothalamic releasing hormones may actually be more widely distributed.

METABOLIC ROLE
In contrast to 'telecrine' action of hypothalamic somatostatin on anterior pituitary, the GI somatostatin has local "paracrine" actions limited to GI mucosa and pancreas.
(a) Hypothalamic Somatostatin:
• Acts as a regulator of growth hormone secretion
• It inhibits GH release
• It may also serve as a neurotransmitter substance in the brain.

(b) Pancreatic Somatostatin:

• It inhibits both insulin and glucagon secretion and thus may serve as an "intra islet" (paracrine) regulator of secretion of these hormones. Thus, acts as intraorgan "synaptic transmitters" or neuromodulators.

• Somatostatin is secreted into the portal vein blood as a result of glucose or amino acid stimulus indicating extra-islet role.

• Also directly inhibit secretion of both HCO_3^- and enzymes in pancreatic juice.

(c) GI Somatostatin:

• Inhibits the secretions of gastrin, CCK, GIP and motilin.

• Also inhibits gastric acid secretion, secretion of Brunner's glands, pancreatic HCO_3^- and enzyme secretions, gastric emptying and gall bladder contraction. Since somatostatin can inhibit a variety of GI functions (gastric emptying, GI motility), its major function may be to regulate nutritional influx at the level of GI tract.

Posttest الاختبار البعدي:

How to control glucose levels in the body

References: المصادر:

BIOCHEMISTRY (Dr. U. Satyanarayana Dr. U. Chakrapani) M.Sc., Ph.D., F.I.C., F.A.C.B. *Professor of Biochemistry & Director (Research)*/Fourth Revised Edition: 2013/ISBN: 978-81-312-3601-7

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Title: **العنوان:**

L 11&12 (ADRENAL GLAND)

Name of the instructor: **اسم المحاضر:**

Assist.prof.Dr. Huda Farhan Ahmed
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Target population: **الفئة المستهدفة:**

Students of the third stage of medical laboratories

Introduction: المقدمة:

The adrenal glands are two small organs (each weighing about 10 g), located above the kidneys. Each adrenal consists of two distinct tissues—an outer cortex (with 3 zones) and inner medulla. As many as 50 steroid hormones (namely adrenocorticosteroids), produced by adrenal cortex, have been identified. However, only a few of them possess biological activity.

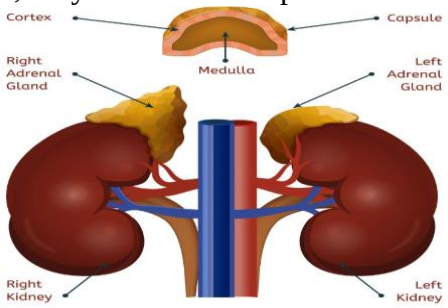
Pretest: الاختبار القبلي:

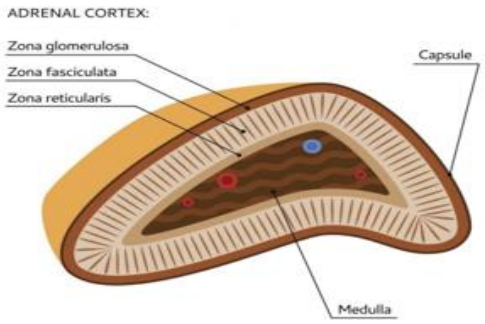
Write the hormones secreted by the adrenal gland?

Scientific Content: المحتوى العلمي:

HORMONES OF ADRENAL CORTEX

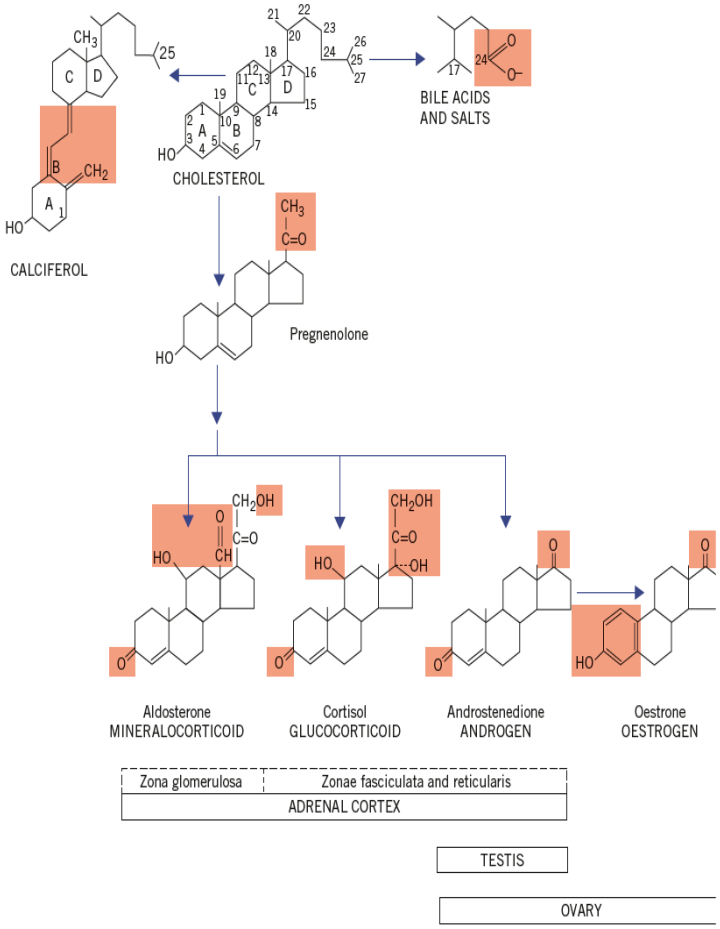
The adrenal glands are two small organs (each weighing about 10 g), located above the kidneys. Each adrenal consists of two distinct tissues—an outer cortex (with 3 zones) and inner medulla. As many as 50 steroid hormones (namely adrenocorticosteroids), produced by adrenal cortex, have been identified. However, only a few of them possess biological activity.





Adrenocorticosteroids are classified into three groups according to their dominant biological action.

1. **Glucocorticoids:** These are 21-carbon steroids, produced mostly by zona fasciculata. They affect glucose (hence the name), amino acid and fat metabolism in a manner that is opposite to the action of insulin. **Cortisol** (also known as hydrocortisone) is the most important glucocorticoid in humans. Corticosterone is predominantly found in rats.
2. **Mineralocorticoids:** These are also 21-carbon containing steroids produced by zona glomerulosa. They regulate water and electrolyte balance. **Aldosterone** is the most prominent mineralocorticoid.
3. **Androgens and estrogens:** The innermost adrenal cortex zona reticularis produces small quantities of androgens (19-carbon) and estrogens (18-carbon). These hormones affecting sexual development and functions are mostly produced by gonads.



Synthesis of adrenocorticosteroids

Cholesterol undergoes cleavage with an elimination of a 6-carbon fragment to form pregnenolone. **Pregnenolone is the common precursor for the synthesis of all steroid hormones**.

Biochemical functions of adrenocorticosteroids

1.Glucocorticoid hormones: The important glucocorticoids are—**cortisol**, **cortisone** and **corticosterone**. They bring about several biochemical functions in the body.

(a) Effects on carbohydrate metabolism: Glucocorticoids promote the synthesis of glucose (gluconeogenesis). This is brought about by increasing the substrates (particularly amino acids) and enhancing the synthesis of phosphoenolpyruvate carboxykinase, the rate limiting enzyme in gluconeogenesis. The overall influence of glucocorticoids on carbohydrate metabolism is to increase blood glucose concentration. The biological actions of glucocorticoids generally oppose that of insulin.

(b) Effects on lipid metabolism: Glucocorticoids increase the circulating free fatty acids. This is caused by two mechanisms.
(i) Increased breakdown of storage triacylglycerol (lipolysis) in adipose tissue.
(ii) Reduced utilization of plasma free fatty acids for the synthesis of triacylglycerols.

(c) Effects on protein and nucleic acid metabolism: Glucocortiocoids exhibit both catabolic and anabolic effects on protein and nucleic acid metabolism. They promote transcription (RNA synthesis) and protein biosynthesis in liver. These anabolic effects of glucocorticoids are caused by the stimulation of specific genes. Glucocorticoids (particularly at high concentration) cause catabolic effects in extrahepatic tissues (e.g. muscle, adipose tissue, bone etc.). This results in enhanced degradation of proteins.

(d) Effects on water and electrolyte metabolism: The influence of glucocorticoids on water metabolism is mediated through antidiuretic hormone (ADH). Deficiency of glucocorticoids causes increased production of ADH. ADH decreases glomerular filtration rate causing water retention in the body.

(e) Effects on the immune system: Glucocorticoids (particularly cortisol), in high doses, suppress the host immune response. The steroid hormones act at different levels—damaging lymphocytes, impairment of antibody synthesis, suppression of inflammatory response etc.

(f) Other physiological effects of glucocorticoids: Glucocorticoids are involved in several physiological functions.
(i) Stimulate the fight and flight response (to face sudden emergencies) of catecholamines.
(ii) Increase the production of gastric HCI and pepsinogen.
(iii) Inhibit the bone formation, hence the subjects are at a risk for osteoporosis.

Mechanism of action of glucocorticoids: Glucocorticoids bind to specific receptors on the target cells and bring about the action. These hormones mostly act at the transcription level and control the protein synthesis.

2. Mineralocorticoid hormones: The most active and potent mineralocorticoid is **aldosterone**. It promotes Na^+ reabsorption at the distal convoluted tubules of kidney. Na^+ retention is accompanied by corresponding excretion of K^+, H^+ and NH_4^+ ions.
Regulation of aldosterone synthesis: The production of aldosterone is regulated by different mechanisms. These include reninangiotensin, potassium, sodium and ACTH.
Mechanism of aldosterone action: Aldosterone acts like other steroid hormones. It binds with specific receptors on the target tissue and promotes transcription and translation.
Metabolism of adrenocorticosteroids: The steroid hormones are metabolized in the liver and excreted in urine as conjugates of glucuronides or sulfates. The urine contains mainly two steroids— 17-hydroxysteroids and 17-ketosteroids—derived from the metabolism of glucocorticoids and mineralocorticoids. Androgens synthesized by gonads also contribute to the formation of **17-ketosteroids**.
Urinary 17-ketosteroids estimated in the laboratory are expressed in terms of dehydroepiandrosterone and their normal excretion is in the range of 0.2–2.0 mg/day.

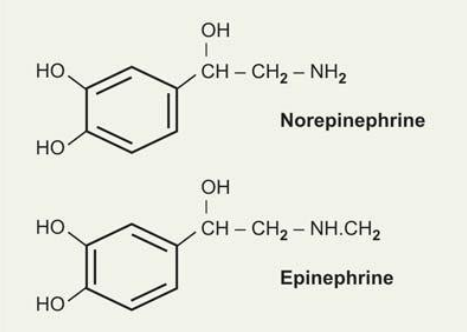
Abnormalities of adrenocortical function

Addison's disease: Impairment in adrenocortical function results in Addison's disease. This disorder is characterized by decreased blood glucose level (hypoglycemia), loss of weight, loss of appetite (anorexia), muscle weakness, impaired cardiac function, low blood pressure, decreased Na^+ and increased K^+ level in serum, increased susceptibility to stress etc.

Cushing's syndrome: Hyperfunction of adrenal cortex may be due to long term pharmacological use of steroids or tumor of adrenal cortex or tumor of pituitary. Cushing's syndrome is characterized by hyperglycemia (due to increased gluconeogenesis), fatigue, muscle wasting, edema, osteoporosis, negative nitrogen balance, hypertension, moon-face etc.

HORMONES OF ADRENAL MEDULLA

Adrenal medulla is an extension of sympathetic nervous system. It produces two important hormones—**epinephrine** (formerly adrenaline) and **norepinephrine** (formerly noradrenaline). Both these hormones are catecholamines since they are amine derivatives of catechol nucleus (dihydroxylated phenyl ring). Epinephrine is a methyl derivative of norepinephrine. Dopamine is another catecholamine, produced as an intermediate during the synthesis of epinephrine. Norepinephrine and dopamine are important neurotransmitters in the brain and autonomic nervous system.



Synthesis of catecholamines

The amino acid tyrosine is the precursor for the synthesis of catecholamines. Catecholamines are produced in response to fight, fright and flight. These include the emergencies like shock, cold, fatigue, emotional conditions like anger etc.

Biochemical functions of catecholamines

Catecholamines cause diversified biochemical effects on the body. The ultimate goal of their action is to mobilize energy resources and prepare the individuals **to meet emergencies** (e.g. shock, cold, low blood glucose etc.).

1. Effects on carbohydrate metabolism: Epinephrine and norepinephrine in general increase the degradation of glycogen (glycogenolysis), synthesis of glucose (gluconeogenesis) and decrease glycogen formation (glycogenesis). The overall effect of catecholamines is to elevate blood glucose levels and make it available for the brain and other tissues to meet the emergencies.

2. Effects on lipid metabolism: Both epinephrine and norepinephrine enhance the breakdown of triacylglycerols (lipolysis) in adipose tissue. This causes increase in the free fatty acids in the circulation which are effectively utilized by the heart and muscle as fuel source.

The metabolic effects of catecholamines are mostly related to the increase in adenylate cyclase activity causing elevation in cyclic AMP levels (refer carbohydrate and lipid metabolisms for more details).

3. Effects on physiological functions: In general, catecholamines (most predominantly epinephrine) increase cardiac output, blood pressure and oxygen consumption. They cause smooth muscle relaxation in bronchi, gastrointestinal tract and the blood vessels supplying skeletal muscle. On the other hand, catecholamines stimulate smooth muscle contraction of the blood vessels supplying skin and kidney. Platelet aggregation is inhibited by catecholamines.

Abnormalities of catecholamine production Pheochromocytomas: These are the tumors of adrenal medulla. The diagnosis of pheochromocytoma is possible only when there is an excessive production of epinephrine and norepinephrine that causes severe hypertension. In the individuals affected by this disorder, the ratio of norepinephrine to epinephrine is increased. The measurement of urinary **VMA** (normal <8 mg/day) is helpful in the **diagnosis** of pheochromocytomas.

Posttest

الاختبار البعدي:

Explain the function of the adrenal medulla

References:

المصادر:

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Introduction: المقدمة:

The gonads (testes in males, ovaries in females) perform closely related dual functions.
1. Synthesize sex hormones;
2. Produce germ cells.
The steroid sex hormones are responsible for growth, development, maintenance and regulation of reproductive system. Sex hormones are essentially required for the development of germ cells.

Pretest: الاختبار القبلي:

What is the germ cells?

Scientific Content: المحتوى العلمي:

GONADAL HORMONES

The gonads (testes in males, ovaries in females) perform closely related dual functions.

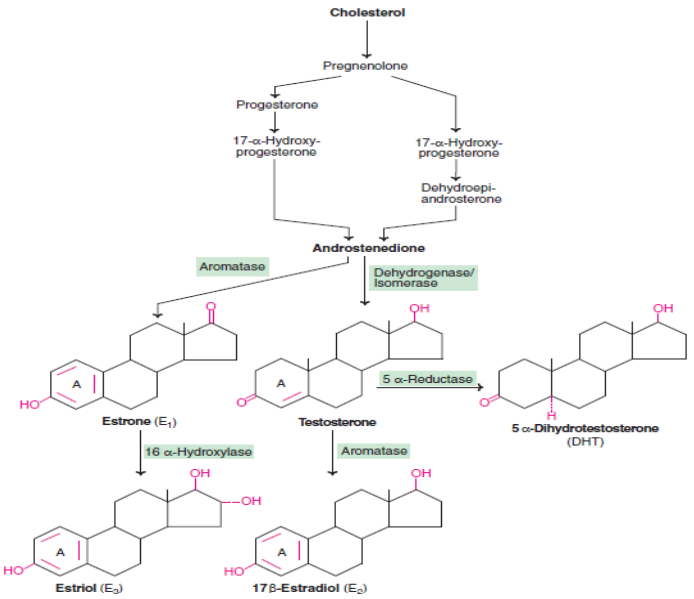
1. Synthesize sex hormones;

2. Produce germ cells.

The steroid sex hormones are responsible for growth, development, maintenance and regulation of reproductive system. Sex hormones are essentially required for the development of germ cells.

The sex hormones are categorized into three groups

1. **Androgens** or male sex hormones which are C-19 steroids.
2. **Estrogens** or female sex hormones which are C-18 steroids. Ring A of steroid nucleus is phenolic in nature and is devoid of C-19 methyl group.
3. **Progesterone** is a C-21 steroid produced during the luteal phase of menstrual cycle and also during pregnancy.



ANDROGENS

The male sex hormones or androgens are produced by the Leydig cells of the testes and to a minor extent by the adrenal glands in both the sexes. Ovaries also produce small amounts of androgens.

Biosynthesis of androgens

Cholesterol is the precursor for the synthesis of androgens. It is first converted to pregnenolone which then forms androstenedione by two pathways—either through progesterone or through 17-hydroxypregnenolone. Testosterone is produced from androstenedione. The production of androgens is under the control of LH and FSH.

Active form of androgen: The primary product of testes is testosterone. However, the active hormone in many tissues is not testosterone but its metabolite **dihydrotestosterone** (DHT). Testosterone, on reduction by the enzyme 5 α-reductase, forms DHT. This conversion mostly occurs in the peripheral tissues. Some workers consider testosterone as a prohormone and dihydrotestosterone, the more potent form as the hormone.

Physiological and biochemical functions of androgens

1. **Sex-related physiological functions:** The androgens, primarily DHT and testosterone, influence:

* Growth, development and maintenance of male reproductive organs.

* Sexual differentiation and secondary sexual characteristics.
* Spermatogenesis.
* Male pattern of aggressive behavior.

2. **Biochemical functions:** Many specific biochemical effects of androgens that ultimately influence the physiological functions stated above are identified. Androgens are anabolic in nature.

* **Effects on protein metabolism:** Androgens promote RNA synthesis (transcription) and protein synthesis (translation). Androgens cause positive nitrogen balance and increase the muscle mass.
* **Effects on carbohydrate and fat metabolisms:** Androgens increase glycolysis fatty acid synthesis and citric acid cycle.
* **Effects on mineral metabolism:** Androgens promote mineral deposition and bone growth before the closure of epiphyseal cartilage.

ESTROGENS

Estrogens are predominantly ovarian hormones, synthesized by the follicles and corpus luteum of ovary. These hormones are responsible for maintenance of menstrual cycle and reproductive process in women.

Synthesis of estrogens

Estrogen synthesis occurs from the precursor cholesterol. Estrogens are produced by aromatization (formation of aromatic ring) of androgens. The ovary produces estradiol (E2) and estrone (E1) while the placenta synthesizes these two steroid hormones and estriol (E3). The synthesis of estrogens is under the control of LH and FSH.

Physiological and biochemical functions of estrogens

1. **Sex-related physiological functions:** The estrogens are primarily concerned with
* Growth, development and maintenance of female reproductive organs.
* Maintenance of menstrual cycles.
* Development of female sexual characteristics.

2. **Biochemical functions:** Estrogens are involved in many metabolic functions.

* **Lipogenic effect:** Estrogens increase lipogenesis in adipose tissue and, for this reason, women have relatively more fat (about 5%) than men.
* **Hypocholesterolemia effect:** Estrogens lower the plasma total cholesterol. The LDL fraction of lipoproteins is decreased while the HDL fraction is increased. This explains the low incidence of atherosclerosis and coronary heart diseases in the women during reproductive age.
***Anabolic effect:** Estrogens in general promote transcription and translation. The synthesis of many proteins in liver is elevated e.g. transferrin, ceruloplasmin.
* **Effect on bone growth:** Estrogens like androgens promote calcification and bone growth. It is believed that decalcification of bone in the postmenopausal women leading to osteoporosis is due to lack of estrogens.
* **Effect on transhydrogenase:** Transhydrogenase is an enzyme activated by estrogen. It is capable of transferring reducing equivalents from NADPH to NAD^+. The NADH so formed can be oxidized. It is explained that in the women after menopause, due to deficiency of estrogens, the transhydrogenase activity is low. This results in the diversion of NADPH towards lipogenesis—causing obesity.

PROGESTERONE

Progesterone is synthesized and secreted by corpus luteum and placenta. Progesterone, as such, is an intermediate in the formation of steroid hormones from cholesterol. LH controls the production of progesterone.

Biochemical functions of progesterone

1. Progesterone is essentially required for the implantation of fertilized ovum and maintenance of pregnancy.

2. It promotes the growth of glandular tissue in uterus and mammary gland.
3. Progesterone increases the body temperature by 0.5–1.5 F°. The exact mechanism of this thermogenic effect is not clearly known. The measurement of temperature was used as an indicator for ovulation.

RELAXIN

Relaxin is a hormone concerned with the relaxation of pelvic tissues and cavity operating in conjunction with other factors. Relaxin is produced, during pregnancy, in tissues of the reproductive system, e.g. ***principally by corpus luteum and also by placenta***. Its production is stimulated by progesterone, pregnenolone and related adrenocortical steroids, e.g. deoxy corticosterone.

Chemistry: Porcine relaxin is made up of two peptide chains, consisting of 22 and 26 amino acid residues. It has two S–S bonds linking its two chains and one intra-chain S–S bond in the A-chain. Approximate mol. wt. = 9000. It is inactivated by proteolytic enzymes or by reagents which breaks the S–S bond (reduction) to form –SH groups.

METABOLIC ROLE

The specific effect of relaxin consists of:

• Increased vascularity of the connective tissue of the symphysis.

• Followed by imbibition of water, dissolution and splitting of collagen fibres, and disorganization of the fibrous structures. There is depolymerization of MPS of ground substance.

• The above makes separation of the symphysis pubis and, a dilatation and softening of uterine cervix, facilitating child birth.

PLACENTAL HORMONES

Pregnancy activates the placental hormones. The implanted blastocyst forms the trophoblast which is subsequently organised into the placenta. The placenta provides the nutritional connection between the embryo and the maternal circulation. ***Human placenta produces and secretes:***

[(a) Peptide hormones and (b) Ovarian steroid hormones]

(a) Peptide hormones:

1. Human chorionic gonadotropin hormone (hCG) and

2. Chorionic somatomammotropin (CS) (also called placental lactogen).

1. Human Chorionic Gonadotropin (hCG):

Origin: It is formed by the syncytiotrophoblast of chorionic villi within 12 to 14 days of fertilization.

Mechanism of Action: The hormone binds to "specific receptor" on the cell membrane of target tissues like ovaries and testes, activates *adenyl cyclase*, which in turn increases cyclic AMP level ↑. Cyclic AMP acts as "second messenger" to produce the biological effects.

METABOLIC ROLE

• ***Luteotrophic effect*:** The hormone produces enlargement of corpus luteum and stimulates its secretion. It maintains a secretory corpus luteum in first three months of pregnancy.

• ***Testosterone secretion:*** Like LH, the hormone stimulates the growth of interstitial cells (Leydig cells) of embryonic testes and produces testosterone. This helps in virilisation of the reproductive system of male embryo.

2. Chorionic Somatomammotropin (CS):(Placental Lactogen)

The hormone has biologic properties of prolactin and growth hormone of anterior pituitary. It is a peptide hormone and amino acid sequences are similar to GH and prolactin (85% homology). ***The hormone is secreted by the syncytiotrophoblast from about the second week of pregnancy,*** rises slowly and reaches

METABOLIC ROLE

The exact role of this hormone is not clear, because pregnant women lacking this hormone have normal pregnancies and deliver normal babies. But as the hormone has similar structure to anterior pituitary GH and prolactin, it exerts similar effects:

• ***Somatotrophic effect:*** May promote growth of maternal tissues.
• ***Luteotrophic effect:*** Stimulates the enlargement, growth and secretion of corpus luteum and helps to maintain a secretory corpus luteum.
• ***Mammotrophic effect:*** Stimulates alveolar growth of mammary glands during pregnancy.
• ***Lactogenic effect:*** Also stimulates lactation.
• ***Anabolic effect:*** Stimulates foetal and maternal tissue growth. Promotes retention of N, Ca++ and inorganic P.
• ***Anti-insulin effect:*** May decrease glucose utilisation, decreased carbohydrate tolerance and hyperglycaemic effect.

(b) Ovarian steroid hormones
1. Progestins
2. Estrogens, chiefly Estriol.

1. Progestins: The corpus luteum is the major source of progesterone for the first 6 to 8 weeks of pregnancy and then placenta takes over this function. The corpus luteum though continues to function, but in third trimester onwards, the placenta produces 30 to 40 times more progesterone than the corpus luteum. ***Placenta cannot synthesize cholesterol from 'active' acetate***, hence for cholesterol it has to depend on maternal supply.
2. Estrogens: Plasma concentrations of estradiol, estrone and estriol gradually increase throughout pregnancy. Estriol is produced in the largest amount. Adrenal cortex of foetus produces DHEA and DHEA SO4, which are converted to 16 α-OH derivatives by the foetal liver, and these are subsequently converted to estriol by the placenta. After its formation, travels via the placental circulation to the maternal liver, where they are conjugated to glucuronides, and then are excreted in the urine.

CLINICAL SIGNIFICANCE

1. Feto-placental function: As estriol is formed by placenta, **the measurement of urinary estriol levels has been used as a test of feto-placental function.** Failure of urinary estriol or total estrogens to rise in late pregnancy reflects the integrity of the feto-placental unit and **may indicate imminent fetal death or placental insufficiency,** e.g preeclamptic toxaemia.

Note: Urinary pregnanediol (or plasma progesterone) reflects placental function only as does estimation of plasma placental lactogen. **A falling titre of urinary estrogens or plasma placental lactogen is serious.**
2. Pregnancy tests: Increased urinary excretion of HCG which occurs in early pregnancy (as early as 10th day of gestation) forms the basis for pregnancy tests.

Posttest الاختبار البعدي:

What are placental hormones?

References: المصادر:

1- **BIOCHEMISTRY (Dr. U. Satyanarayana Dr. U. Chakrapani) M.Sc., Ph.D., F.I.C., F.A.C.B.** ***Professor of Biochemistry & Director (Research)*****/Fourth Revised Edition: 2013/ISBN: 978-81-312-3601-7**
2- **Textbook of Medical Biochemistry Eighth Edition 2012. MN Chatterjea Rana Shinde**

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Students of the third stage of medical laboratories

Introduction: المقدمة:

Several other glandular tissues are considered to secrete hormones, viz.:(***JG cells of kidney, Thymus, Pineal gland and GI tract.***

Pretest: الاختبار القبلي:

What do glandular tissue hormones mean?

Scientific Content: المحتوى العلمي:

Several other glandular tissues are considered to secrete hormones, viz.**:(** ***JG cells of kidney, Thymus, Pineal gland and GI tract.***

• *JG cells of kidney:* May produce the hormone ***erythropoietin*** which regulates erythrocyte maturation, erythropoiesis.
A distinct aspect of renal endocrinology relates to the production of erythropoietin (EPO), and the regulation of erythropoiesis. Erythropoietin (EPO) is a hormone secreted by juxtaglomerular cells in the kidney that stimulate the bone marrow to manufacture red blood cells (erythrocytes).Fibroblasts in the kidney are always making erythropoietin to keep the bone marrow active in making new red blood cells to replace the aging ones.
Red blood cells in the blood stream contain hemoglobin that transport oxygen from air in the lungs and deliver it to every cell in the body. Those red blood cells are produced in the bone marrow and have a lifespan of about three months. When the oxygen delivery system fails to deliver adequate oxygen, whether it is because of a lack of adequate red blood cells (anemia), or lack of available oxygen (hypoxia), the kidney fibroblasts increase their production of erythropoietin.
The kidney may increase erythropoietin levels in patients with chronic anemia, patients with COPD who have chronically low blood oxygen levels, or in people who live at high altitude where there is less oxygen in the air. Patients who have chronic kidney disease may not be able to produce adequate amounts of erythropoietin leading to anemia.

• ***Thymus:*** This produces a hormone that circulates from this organ to stem cells in lymphoid organ inducing them to become immunologically competent lymphocytes.
The thymus gland is a soft organ that is large in babies but begins to shrink after puberty. Once you reach adulthood, your thymus gland becomes relatively small. Thymus gland is between your ascending aorta and sternum. It is in the space between your lungs, which is also home to your heart, esophagus, and lymph nodes.
The main function of your thymus gland is to process and teach your T cells. Inside your thymus, these T cells don't react to bacteria or viruses. After these cells mature, they go into the blood and defend your lymphatic organs from disease.
Another essential function of your thymus gland is to produce the hormone thymosin. This hormone helps mature T cells in other organs. Other hormones your thymus gland makes include:

- Thymopoietin
- Thymulin
- Thymic humoral factor

The thymus functions as an area for diverse T cells to learn how to identify and get rid of foreign organisms in your body. Your thymus plays a significant role in keeping your immune system robust and defendable.

• *Pineal gland:* It produces a hormone that antagonises the secretion or effects of ACTH. It also produces factors called **glomerulotrophins** that regulates the adrenal secretion of aldosterone.
The pineal gland (or pineal body) is a small organ that lies within the roof of the third ventricle, deep within the brain. Autopsy studies have shown that the average size of the pineal gland is similar to that of a grain of rice.
It is located within an area called the epithalamus, just behind the thalamus and above the cerebellum, resting at the back of the brain, near the brain stem. A small fluid-filled structure projects into the pineal gland, allowing the hormones it produces to more easily diffuse throughout the brain.

The pineal gland is a neuroendocrine organ located in the brain that primarily produces melatonin, a hormone released in response to a lack of light. It is responsible for the body's circadian rhythms.
Like all parts of the endocrine system, the pineal gland makes hormones. The hormones produced by organs and glands of the endocrine system control vital functions like growth, development, reproduction, metabolism, and more

Mechanism

The rate-limiting step that helps this is process is controlled by the enzyme serotonin N-acetyltransferase (NAT). This enzyme, which is needed to synthesize melatonin from serotonin, is low during daylight hours. Serotonin is the precursor of melatonin. Serotonin is also derived from an amino acid called tryptophan. In the pineal gland, serotonin undergoes acetylation and then methylation to yield the end product of melatonin. Melatonin then reacts with G- protein receptors to implement the biological effects that are needed. These receptors are found in the suprachiasmatic nucleus of the hypothalamus, the retina, and the pars tuberalis in the adenohypophysis. Receptors are also scattered around various areas of the brain. Melatonin binds to albumin in the human plasma.

• ***GI tract:*** Few hormones are also produced by certain specialised cells of GI tract and they are called GI Hormones. The specialized cells lining the GIT are responsible for the production of GIT hormones. Hence GIT may be considered as the largest mass of cells that secrete hormones. A large number of GIT hormones have been identified. However, only four GIT hormones have been well characterised.

1. **Gastrin:** This hormone contains 17 amino acids and is produced by gastric mucosa. It stimulates the secretion of gastric HCI and pepsinogen (proenzyme of pepsin). The release of gastrin is stimulated by vagus nerve of stomach and partially digested proteins. HCI and certain other hormones inhibit gastrin release.

2. **Secretin:** It is a 27-amino acid containing polypeptide and resembles glucagon in many ways. Secretin is synthesized by the mucosa of the upper small intestine. It is released in response to the presence of HCI in chyme in the duodenum which is passed on from the stomach. Secretin stimulates pancreatic cells to produce bicarbonate (HCO_3^-) in order to neutralize HCI.

3. **Cholecystokinin (CCK):** It contains 33 amino acids and is produced by the upper part of small intestine. The secretion of CCK is stimulated by the products of protein and lipid digestion, namely peptides, amino acids, mono or diacylglycerols, fatty acids and glycerol. Cholecystokinin stimulates the contraction of gall bladder and increases the flow of bile into duodenum. It also promotes the secretion of digestive enzymes and HCO_3^- from pancreas.

4. **Gastric inhibitory peptide (GIP):** It contains 43 amino acids and is produced by duodenal mucosa. The release of GIP is stimulated by the presence of glucose in the gut. The most important function of GIP is to stimulate the release of insulin from pancreas. This is evident from the fact that the plasma insulin level is elevated much before the increase in blood glucose. GIP also inhibits gastric HCI secretion, gastric motility and its emptying. GIT hormones show certain structural relations and may be considered under two families.

(i) **Gastrin family:** Some of the C-terminal amino acids are identical. This family includes gastrin and CCK.

(ii) **Secretin family:** Secretin, GIP and glucagon are structurally related, hence may be considered under this family. Besides the hormones described above, several other hormones (in hundreds!) from the GIT have been identified. These hormones are often known as **candidate hormones,** since their biological functions are yet to be precisely identified. The candidate hormones include **vasoactive intestinal peptide** (VIP), **motilin, enteroglucagon, substance P, neurotensin, somatostatin** and **enkephalins**.

Mechanism of action of GIT hormones

Many of the GIT hormones have receptor sites specific for their action. At least two distinct mechanisms have been identified through which these hormones act.

1. Production of cAMP through the activation of adenylate cyclase e.g. secretin, VIP etc.
2. Stimulation of intracellular Ca^{2+} usually mediated through the metabolism of phosphatidylinositol e.g. gastrin, CCK. Both these mechanisms ultimately influence the enzyme secretions/other biological effects.

Posttest

لاختبار البعدي:

Write down what you know about stomach hormones

References:

المصادر:

BIOCHEMISTRY (Dr. U. Satyanarayana Dr. U. Chakrapani) M.Sc., Ph.D., F.I.C., F.A.C.B. ***Professor of Biochemistry & Director (Research)*****/Fourth Revised Edition: 2013/ISBN: 978-81-312-3601-7**