PHYSIOLOGY

Sheet 10

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We've talked in the previous lecture about desensitization and how it affects the hormone's function.

- Also, we have two types of desensitization: homologous & heterologous desensitization.

Desensitization it is when the cells are exposed to a certain hormone for a long duration, at the end the cells won't respond properly to that hormone because: **1)the number of receptors decreased** as well as **2)the affinity of these receptors** to that hormone.

- In this case when the number of receptors in the target cell have decreased, this is called **Down regulation.**

An example on down regulation is **Diabetes Mellitus** (Type 2)

In which glucose levels in blood are high, insulin levels are also high, but insulin isn't functioning properly.

So usually these patients could be:

- Usually old patients are obese (above 45)
- Sometimes young and obese
- Sometimes young but not obese

- The only possible treatment for diabetes is by **exercising** & changing eating habits in order to **lose weight.**

As a result, the number of receptors increases as well as the affinity of these receptors to that hormone, this is called **upregulation**.

The ideal way of exercise is by walking 10min/km (1h/6km), and swimming. But exercise is not enough to treat diabetes unless these patients lose weight.

Diabetes mellitus type 2 patients are advised to follow up a diet and link it with exercising

Changes in rates of receptor synthesis may also contribute to long-term downregulation or upregulation.

HORMONAL INTERACTIONS

Hormones don't function separately.

Example: the growth hormone (GH) functions ONLY in the presence of the hormone insulin.

There are 3 types of hormonal interactions:

1- Permissive hormonal interaction

when the hormone needs the action of another hormone to function properly**.**

Example:

Fat cells are affected by both thyroxine & adrenaline.

A Fat cell when affected by thyroxine ➔ No release of fatty acids

The same fat cell when affected by adrenaline ➔ Fatty acids are released

The same fat cell affected first by thyroxine then adrenaline ➔ Functioned properly.

It means for the adrenaline to function properly first it needs the effect of thyroxine then adrenaline.

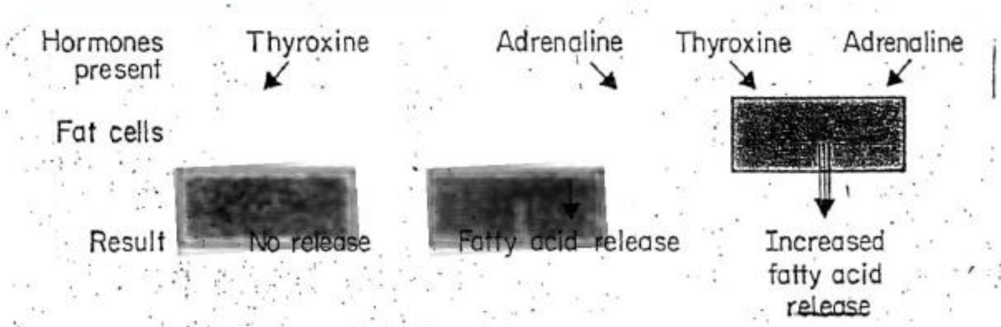


Fig. 11.1 Specific action of one hormone depends on the 'permissive' presence of another.

One type of interaction is referred to as a ***permissive effect.*** In this interaction, the effect of one hormone on a target cell requires a previous or simultaneous exposure to another hormone(s). Such previous exposure enhances the response of a target cell or increases the activity of another hormone. An example of a permissive effect, as noted earlier, is the exposure of the uterus first to estrogens and then to progesterone in order to prepare the organ for implantation.

2-Synergistic hormonal interaction

when one or two of the participating hormones is/are absent then the result will be defected (when two or more hormones are functioning together, each one is complementary to the other).

In this way, the target cell responds effectively to the sum of hormones involved.

Example: the production and secretion of milk by mammary glands requires the action of estrogen, progesterone, oxytocin and prolactin.

3-Antagonistic hormonal interaction

When the effect of one hormone on the target cell is opposed by another hormone.

Example:

1) Insulin & Glucagon they have opposite functions on glucose levels in blood, in which insulin decreased glucose levels while glucagon increases glucose levels.
2) Calcitonin & Parathyroid hormones, in which calcitonin lowers calcium levels while parathyroid hormones raise calcium levels.

CHEMISTRY OF HORMONES

Recall: we have 3 Types of hormones according to their chemical composition:

1) Protein (most of hormones are proteins)
2) Amino acid derivatives
   Such as: Catecholamines & thyroid hormones
3) Steroids

Such as human sex hormones

To begin with, protein hormones **are large hormones,** so they cannot penetrate/cross cell membranes, so their **receptors are found on the cell's surface.**

Each hormone has a specific receptor on its target cell. But sometimes, we may have some hormones that can bind to 2 receptors.

- So, hormones need receptors to function. Also, hormones can produce second messengers.

1)When the protein hormone binds to its specific receptor which is on the cell membrane, that leads to the formation of the **Hormone-Receptor Complex.**

2) The hormone receptor complex activates the G-protein in the cell membrane.

Recall: each G- protein is composed of 3 subunits alpha, beta and gamma

3) When the hormone receptor activates this G- protein, the alpha subunit separates which is the **active part of G-protein**, then alpha goes and bind to GTP and together they activate adenylyl cyclase

4) When the adenylyl cyclase gets activated it will produce cyclic AMP from ATP and this **is the second messenger**

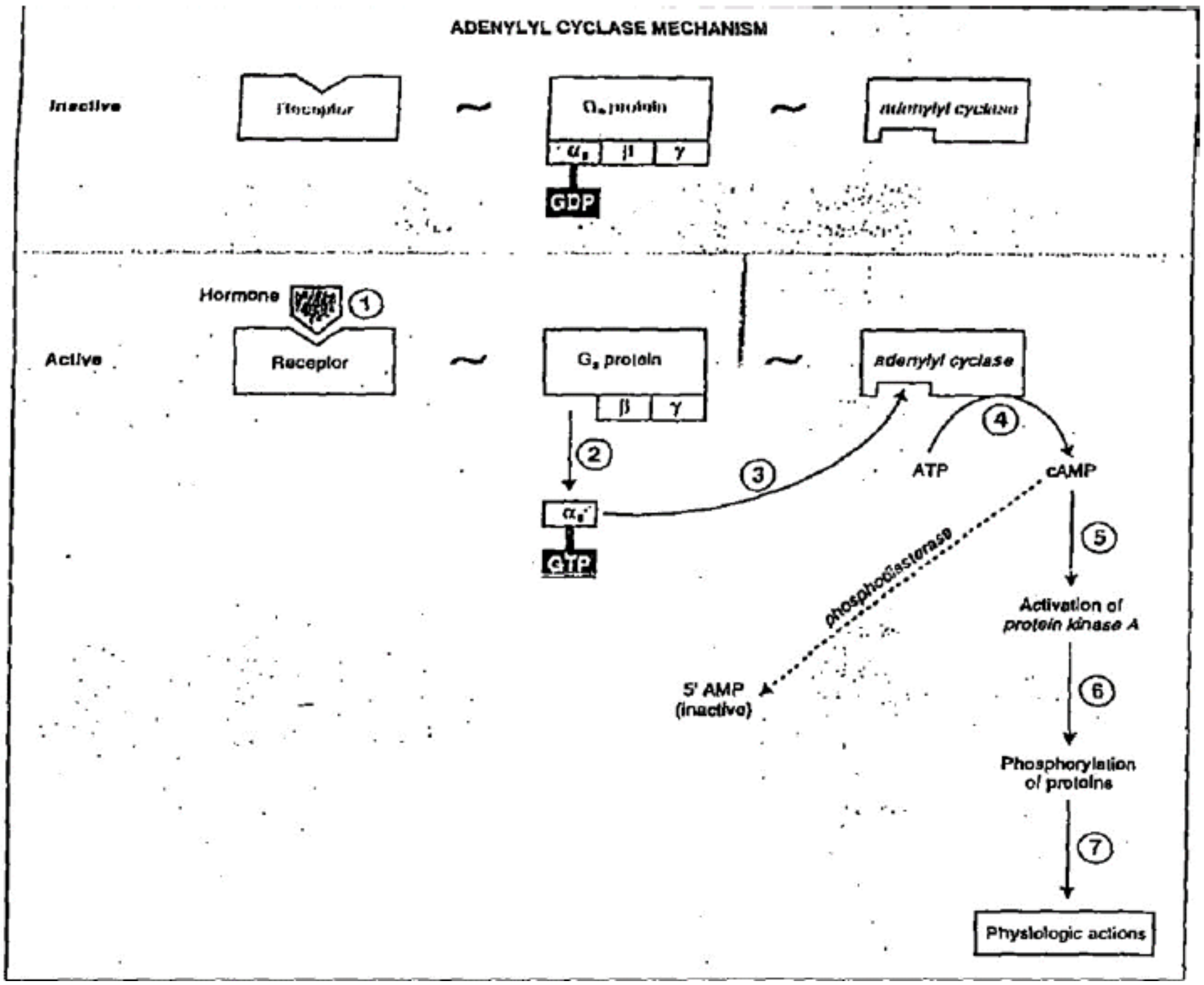
5) cAMP goes and activates other protein that represents the response of the hormone

Table 74-2 Hormones That Use the Adenylyl Cyclase–cAMP Second Messenger System

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

When the hormone binds to its specific receptor but doesn't product cAMP, this hormone cannot perform its function

*Sometimes when there is too much of cyclic AMP, the extra cyclic AMP will be inactivated **by phosphodiesterase enzyme**.*



- Some protein hormones to function they need to produce two second messengers like; IP3 and DAG.

So, activation of Inositol triphosphate (IP3) and diacylglycerol (DAG) needs two second messengers and Ca, to function properly.

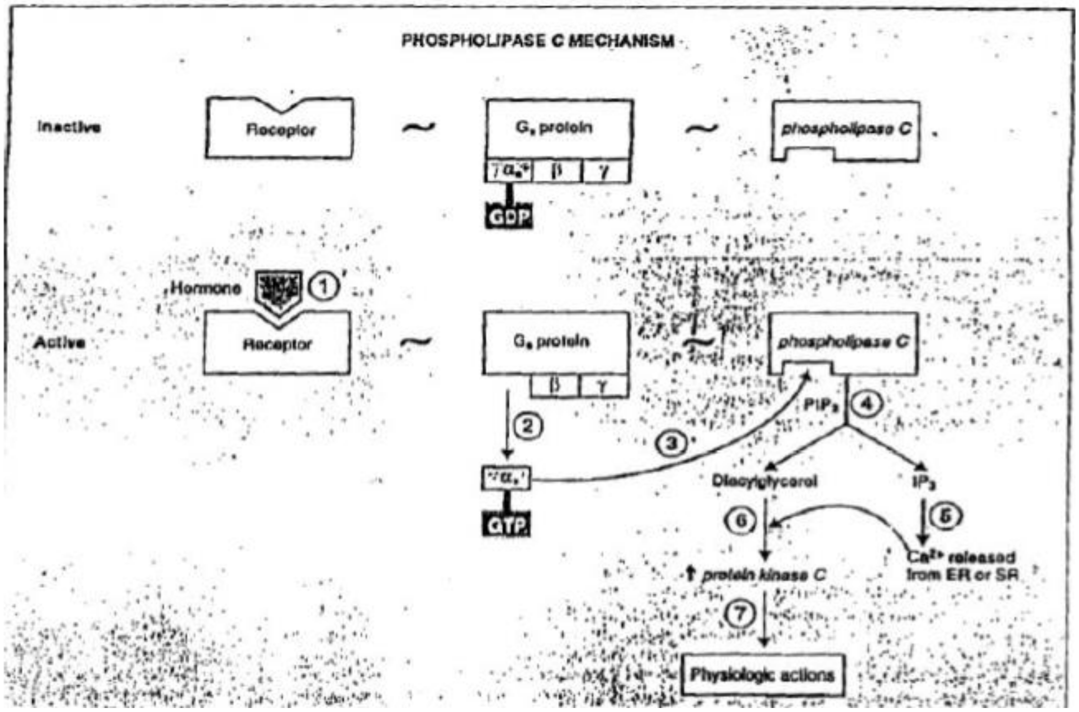
Table 74-3 Hormones That Use the Phospholipase C Second Messenger System

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

➢ The same G-protein instead of activating adenylyl cyclase it activates **phospholipase C**, but two second messengers are produced:

1) Diacylglycerol (DAG) ➔ for the activation of the enzyme

2) Inositol triphosphate (IP3)➔ to increase the calcium



Amino Acid derivatives hormones

amino acid derivatives are **small** molecules they are lipid soluble; they **can penetrate cell membrane as well as nuclear membrane**, they could be either:

1) Catecholamines such as: dopamine, adrenaline and noradrenaline they serve as neurotransmitters in brain.

2) Thyroid hormones

Why Catecholamines like adrenalin (one of its amino acids is tyrosine DON'T PENTRATE THE CELL MEMBRANE OR THE NUCLEAR MEMBRANE WHILE THYRIOD HORMONES (two amino acids ➔ two tyrosine) DO??

Because the neurotransmitters are hydrophilic molecules, they are unable to cross the plasma membrane of their target cells. Therefore, in contrast to thyroid hormones are lipid soluble.

Steroid Hormones

Steroids hormones and thyroid hormones are lipid soluble also they can penetrate the cell and nuclear membranes

Sometimes they find their receptors in the cytoplasm but most commonly in the nucleus **affect the DNA** that is producing the mRNA then physiological response occur.

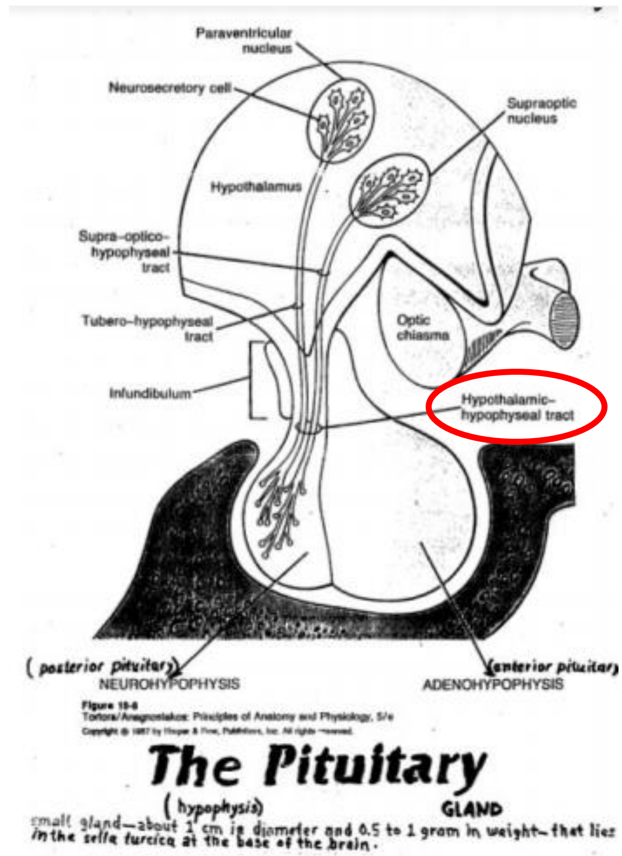
➢ Steroid hormones include:

Male hormones, female hormones, adrenalin cortex hormone

Sometimes these steroid hormones must function immediately (rapid reaction), they have their receptors on the surface of target cells.

Such as: estrogens and progesterone

THE PITUITARY GLAND -ALSO CALLED HYPOPHYSIS GLAND



In the past, the pituitary gland was called the master gland but not anymore. Now, hypothalamus is the master gland.

Master gland means mastering all the glands/controlling them.

The pituitary gland properties:

- Very small (about 1 cm in diameter)
- Weights 1 gram or less
- It's present inside a cavity (sella turcica)
- Composed of 2 parts
  - Anterior pituitary/ Adenohypophysis
  - Posterior pituitary/ Neurohypophysis

These 2 differ in their embryology, physiology and histology

These 2 parts are either connected to the hypothalamus directly (like the posterior pituitary) or indirectly.

The hypothalamus is connected to the pituitary by the <u>hypothalamic – hypophyseal tract</u>

You can see from the picture above neurons that extend from hypothalamus to the posterior pituitary gland which means that the hormones that are in the posterior pituitary are originally from the hypothalamus.

So, the function of the posterior pituitary gland is ➔ storage function ONLY.

The hormones in the posterior pituitary are called neurohormones and the posterior pituitary is called the neuroendocrine gland.

There are 2 hormones are in the posterior pituitary: ***Oxytocin*** and ***ADH (antidiuretic hormone)***

Oxytocin is released from cells known as the paraventricular nucleus; the site where Oxytocin is produced and *some* ADH.

The 2nd hormone, ADH, is produced from another nucleus called Supraoptic (and *some* Oxytocin is produced from it as well).

What do we conclude from this?

That these two hormones are somehow similar in structure and function. BUT the similarity in structure is more than the similarity in function. Structurally, they differ in only 2 amino acids.

The function	ADH (vasopressin)	Oxytocin
Water reabsorption	200	1
Milk ejection	1	100

In milk ejection (which is the main function of oxytocin) the ratio is 100:1

Remember the function of oxytocin is milk production and release, as well as uterine contraction during baby delivery.

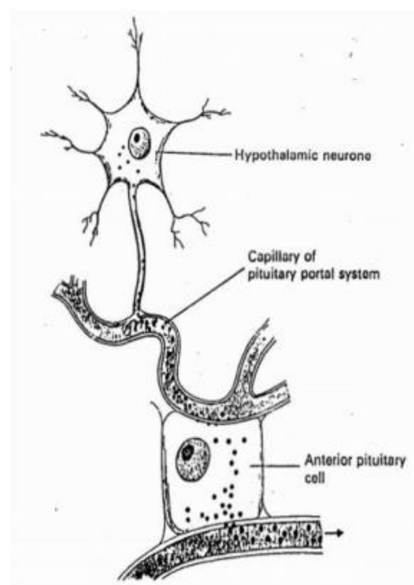
ADH/vasopressin mainly acts on kidney tubules and normalize the reabsorption of water back into the blood/body fluid volume. It also affects the vasoconstriction of the blood vessels- thus it is called vasopressin.

- Note that the receptors of ADH/Vasopressin on the kidney tubules differ from the receptors on the blood vessels. Therefore, we have vasopressin 1 receptors (V1) and vasopressin 2 receptors (V2).

Factors that affect ADH secretion:

Stimulatory Factors	Inhibitory Factors
Increased serum osmolarity	Decreased serum osmolarity
Decreased ECF volume	Ethanol
Pain	α-Adrenergic agonists
Nausea	Atrial natriuretic peptide (ANP)
Hypoglycemia	
Nicotine	
Opiates	
Antineoplastic drugs	

Remember that the posterior pituitary is directly connected to the hypothalamus while the anterior pituitary isn't directly connected. Therefore, hormones that are released from the hypothalamus do not affect the anterior pituitary directly *so how can they reach it?*



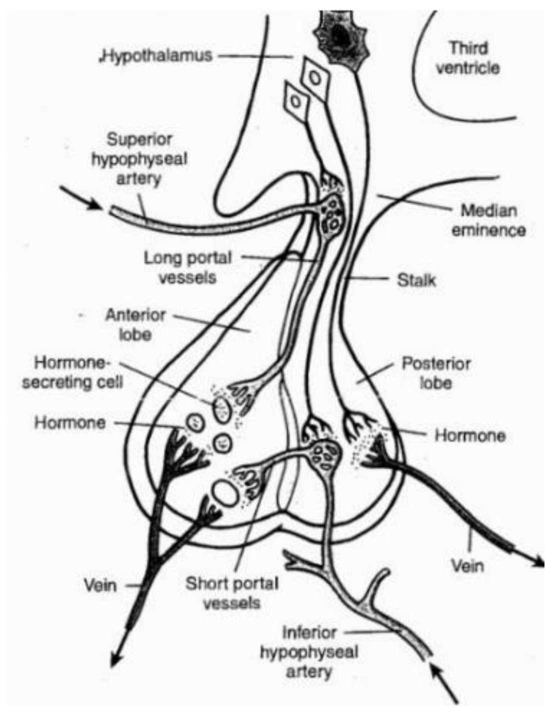
First hormones secreted from the hypothalamus are released into a capillary bed in a location called the median eminence and are stored there. Then they are stimulated and so they are released to affect the anterior pituitary.

Immediate release of the hormones to affect the anterior pituitary gland is through the short portal vessels which are close to the posterior pituitary gland. The long portal vessels come from the median eminence.

To help you understand better: (from Guyton's p.941)

Hypothalamus has special neurons that originate from various parts of the hypothalamus and these neurons synthesize and secrete hypothalamic releasing and inhibitory neurons that control the anterior pituitary. It sends their nerve fibers to the median eminence (part of the hypothalamus from which regulatory hormones are released, it connects the hypothalamus to the pituitary). Note that the ending of these fibers are different from what we took before; they do not transmit signal from one neuron to the other. They help to secrete the hormones into the portal systems (long/short vessels) to the pituitary.

Short loops help to get a quick response and release while the long loop takes longer time.



- **Through short portal vessels:**

Hypothalamus → downwards →to a location just beside the posterior pituitary → stimulate anterior pituitary hormone

- **Through long portal vessels:**

Median eminence → stimulate anterior pituitary.

The anterior pituitary gland contains several cell types that synthesize and secrete hormones. Usually there's one cell type for each major hormone but there are exceptions. There's at least 5 cell types.

*you have to memorize this table

Cell	Hormone	Chemistry	Physiological Action
Somatotropes	Growth hormone (GH) (somatotropin)	Single chain of 191 amino acids	Stimulates body growth; stimulates secretion of insulin-like growth factor-1; stimulates lipolysis; inhibits actions of insulin on carbohydrate and lipid metabolism
Corticotropes	Adrenocorticotropic hormone (ACTH) (corticotropin)	Single chain of 39 amino acids	Stimulates production of glucocorticoids and androgens by the adrenal cortex; maintains size of zona fasciculata and zona reticularis of cortex
Thyrotropes	Thyroid-stimulating hormone (TSH) (thyrotropin)	Glycoprotein of two subunits, α (89 amino acids) and β (112 amino acids)	Stimulates production of thyroid hormones by thyroid follicular cells; maintains size of follicular cells
Gonadotropes	Follicle-stimulating hormone (FSH)	Glycoprotein of two subunits, α (89 amino acids) and β (112 amino acids)	Stimulates development of ovarian follicles; regulates spermatogenesis in the testis
	Luteinizing (LH) hormone	Glycoprotein of two subunits, α (89 amino acids) and β (115 amino acids)	Causes ovulation and formation of the corpus luteum in the ovary; stimulates production of estrogen and progesterone by the ovary; stimulates testosterone production by the testis
Lactotropes-Mammotropes	Prolactin (PRL)	Single chain of 198 amino acids	Stimulates milk secretion and production

30-40% of the anterior pituitary are somatotropes that secrete growth hormone while 20% are corticotropes. Each of the other cells are 3-5% but their hormones are still important.

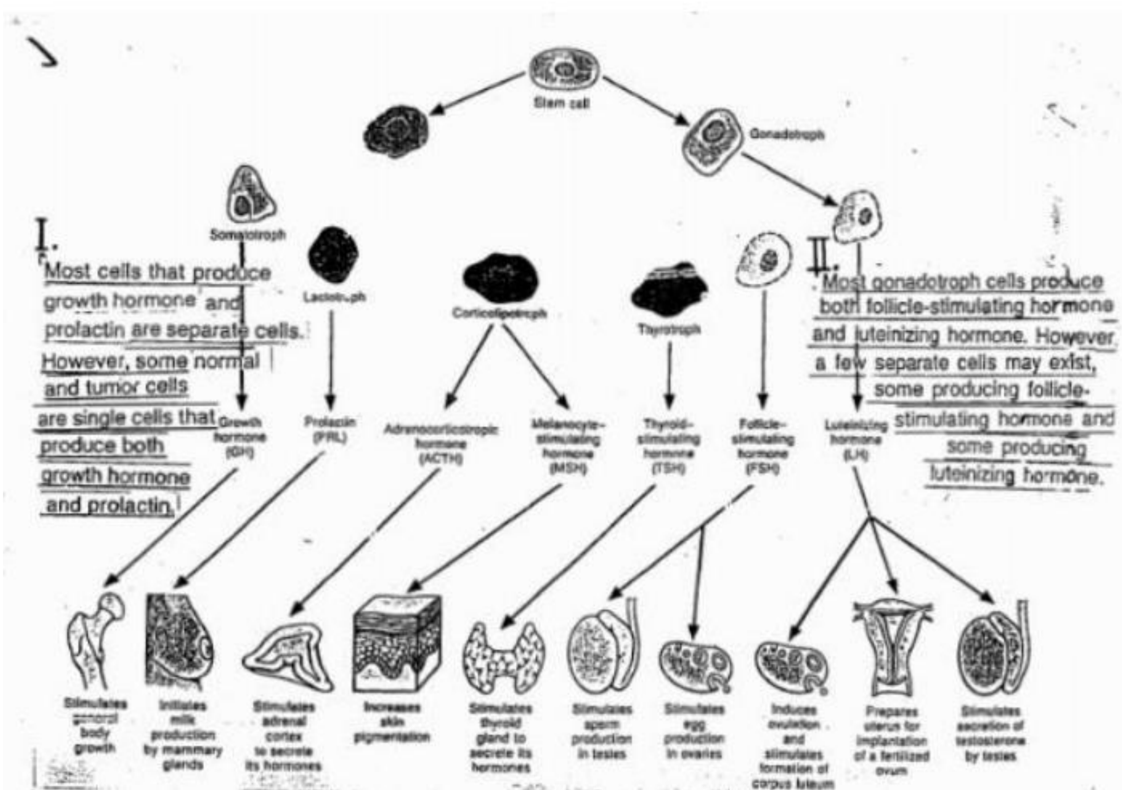


FIGURE 18-6 Cells of the adenohypophysis as revealed by special strains.

We have somatotopes that secrete GH and lactotopes that secrete prolactin but in some normal and abnormal conditions we can find one cell that secretes both GH and prolactin. Also, we have Gonadotropes that secrete both FSH and LH but we can find a cell that secretes FSH only and another type of cell that secretes LH only.

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

Remember that hypothalamus releases hormones that affect the anterior pituitary hormones.

All stimulatory hormones of the anterior pituitary gland are more important than the inhibitory hormones except prolactin. ***Why?*** Because prolactin is not needed in both sexes and even in females it is not always needed (only during pregnancy and delivery).

Many hormones that function together complement each other.

Growth hormone does not function properly unless insulin is present.

Synergistic effect: An effect arising between two or more agents, entities, factors, or substances that produces an effect greater than the sum of their individual effects

Multiple hormones function in a synergistic pattern to cause growth including: growth hormone (GH), insulin – like growth factors (IGF-I and -II), insulin, thyroid hormones,

Glucocorticoids, androgens & estrogens contribute to the growth process in humans.

Among these, GH & IGF-I have been implicated as the major determinants of growth in normal post-uterine life. However, deficiencies (or excesses) of each of the other hormones can seriously affect the normal growth of the musculoskeletal system as well as the growth and maturation of other tissues.

Good Luck!