COMPARATIVE PHYSIOLOGY

For

B.SC. STUDENTS

zoology

BY

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CONTENT

(A)

NERVOUS CONTROL SYSTEM

INTRODUCTION

The nervous system along with the endocrine system, provides most of control functions for the body.

The nervous system can be said to comprise the nerves, the ganglia with which they are connected, and the mass of tissue from which they emerge. Expressed in cellular terms this would include all the nerve cell bodies, their processes (fibers, tracts, etc.) and supporting cells and membranes. Physiologically speaking the nervous system is that component of a living system which is specialized for carrying information and for integrating the reactions to the environment.

The nervous system is usually divided into central and peripheral parts. The central nervous system (CNS) comprises the parts contained within the skull and vertebral column, while the latter term includes the ganglia and the fiber bundles which connect the central portion of the system with the sense organs and with the effectors of the body (muscles, glands, etc.). The central part may further be subdivided into the brain (contained within the skull) and the spinal cord (contained within the vertebral column). The peripheral parts subdivided into cranial and spinal nerve.

The spinal nerves are connected to the CNS by two roots (ventral and dorsal), while cranial nerves are variable in their connected to these nerves are actually bundles of fibers, each connected single nerve cell body.

One can furthermore distinguish an autonomic nervous system, which consists of an aggregation of nerves and ganglia through which the heart, blood vessels, viscera, glands, etc. receive their innervation. These organs which are regulated "involuntarily" receive a double innervation, one component from the sympathetic and the other from the parasympathetic division of the autonomic nervous system. The actions of the two are generally opposite, so that the activity level of these organs is determined by the relative strengths of excitatory and inhibitory nerve actions upon it.

NERVOUS SYSTEM

Nervous system consists of the following:-

1-The central nervous system.

2-The peripheral nervous system.

3-Autonomic nervous system.

1-The central nervous system composed of:-

A-The brain B-The spinal cord.

2-The peripheral nervous system which composed of the nerves extending from the central nervous and include:

A. Cranial nerves B. Spinal nerves.

3-The autonomic nervous system Is classified into two part:

A) Sympathetic nervous system: is made up of two chains of nerve ganglia lying on both sides of the vertebral column.

B) Para-sympathetic nervous system: The bodies of its pre-ganglionic neurons lie in CNS.

The para-sympathetic ganglia differ from the sympathetic ones in:

1-They are fewer in number.

2-Larger in size.

3-And are situated near, on or in the walls of different viscera (while sympathetic ganglia lie very close to the CNS far from the viscera).

THE NERVE CELL

The basic unit of the nervous system is the individual nerve cell or neuron.

The neuron, as a cell, consists of a cell body with from one (unipolar) to several (multipolar) processes.

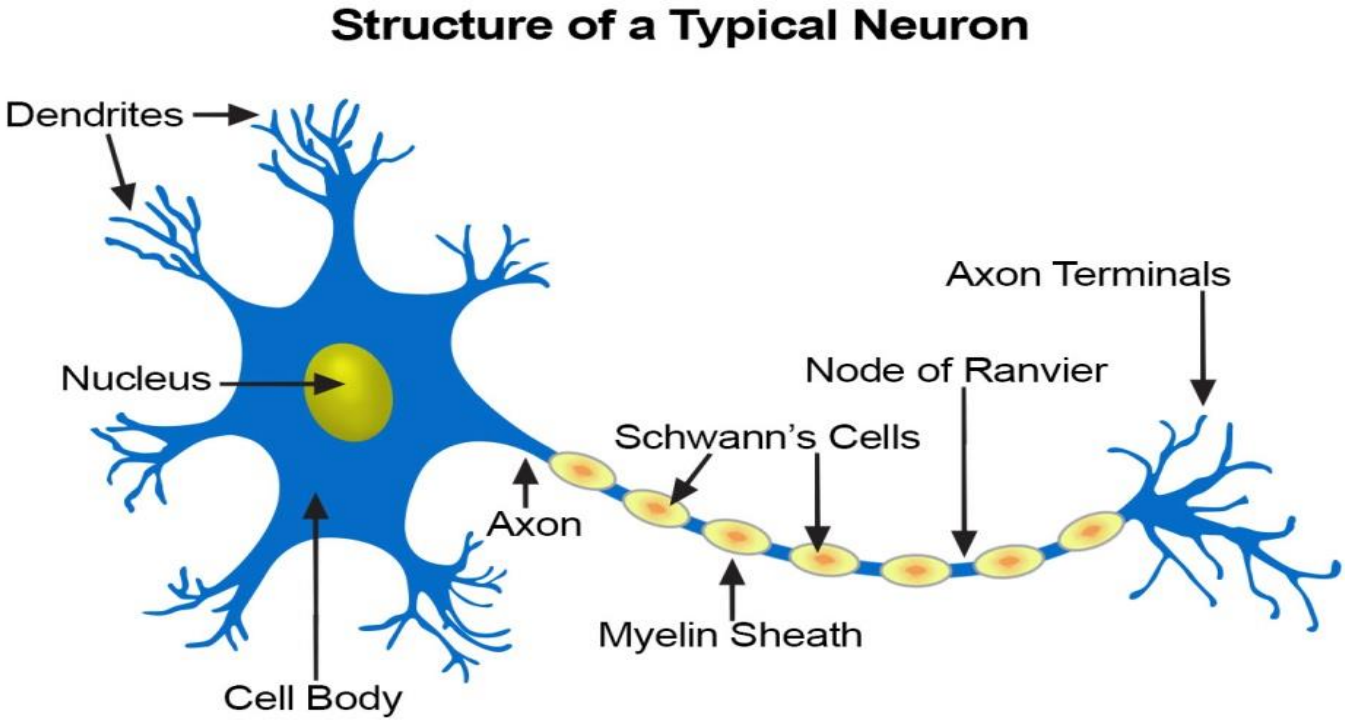
Nerve cells possess the particular of being able to conduct and transmit impulses. They synthesize neurotransmitters such as acetylcholine, catecholamines and indoleamines. They are also involved in lipid. Carbohydrate and protein synthesis. All neurons have a high metabolic rate and they require a constant supply of O_2 and glucose as well as other nutritional components.

The processes of nerve cells have been classified as being of two sorts. One, the dendrite, transmits generally an impulse toward the cell body or soma and the other, the axon, transmits an impulse away from the soma.

The cell bodies of neurons are fundamentally the soma as all other cells. They are enclosed within a cell membrane and contain a nucleus and nucleolus, mitochondria, Golgi substance, endoplasmic reticulum and ribosomes, fibrils (neurofibirils) and micro vesicles. It should be noted that, in the neuron, the endplasmic reticulum and the ribosomes are associated together to form a chromophilic structure recognized by light microscopy as Nissl substance. All the evidence suggest that the endoplasmic reticulum with its RNA is connected with synthesis of various materials, under the influence of the nucleus.

The axon of a neuron is very delicate structure often protected and strengthened in vertebrates by being surrounded by cells known as Schwann cells. Some nerves have these cells developed in a remarkable manner, the cells being wounded around the axon several times.

The result is that the axon is surrounded by numerous layers of the plasmalemma of the Schwann cell. The layers of lipoprotein membrane known collectively as the myelin sheath of the neuron. The sheath provides electrical insulation and myelinated nerves usually conduct signals faster than nonmyelinated ones.



are small gaps between the Schwann cells, known as nodes of Ranvier. Here the axon comes into direct contact with the normal extracellular fluid of the animal.

Types of Neurons:

According to the number of processes arising from the cell body, a neuron is termed unipolar, bipolar or multipolar. The unipolar neuron having only one true process, an axon, which divides into peripheral and central branches (e.g. sensory neuron of spinal ganglion). The bipolar neurons are characteristically found in the retina, where the two processes emerging from the cell-body are both described as axons. Typical multipolar neuron is the major neuron seen, characteristically, in the ventral horn of the cord. It is a large cell with many dendrites and an axon that terminates on one or more muscle fibers.

From a functional standpoint we may classify the neurons as **(a) sensory, (b) effector or motor, and (c) connector neurons (interneurons)**.

Central Nervous System

The central nervous system is composed of the brain and the spinal cord.

A. Brain

The brain is composed of six subdivisions: cerebrum, diencephalon, mid-brain, pons, medulla and cerebellum. The midbrain, pons and medulla together from the brainstem, whereas the cerebrum and diencephalon together constitute the forebrain.

1-Forebrain:

it is consists of a central core (the diencephalon) and the right and left cerebral hemispheres (the cerebrum). The hemispheres, although largely separated by a longitudinal division, are connected to each other by axon by bundles known as commissures, the corpus callosum.

The outer part of the cerebral hemispheres, the cerebral cortex or gray matter, is a cellular shell about 3 mm thick, covering a dense thick inner layer of white matter. There are three main areas in the cerebral cortex, these are ***sensory***, ***motor*** and ***association areas***.

Sensory areas:

Receive an coordinate impulses sent by the sense organs, such as vision or hearing.

Motor areas:

Generate impulses that travel out to the voluntary muscles of the body and stimulate eye movements, speech, walking, swimming, writing and many other complex body motion.

Association areas:

Certain association areas are connected with speech, while others control memory, reasoning power, judgment and emotions such as love, fear and anger.

The thalamus, part of the diencephalon, is a region of gray matter that relays impulses between the cerebral cortex and spinal cord. It is also thought that subjective feelings as pleasure or pain and likes or dislikes, are determined here.

The hypothalamus, is a mass of gray matter found beneath the thalamus. It is concerned with a variety of functions, including regulation of the heart beat and the body's metabolism of carbohydrates, fats and water. It is also important in regulating sleep and in controlling emotions and sensivity to sexual excitement. Indeed, the hypothalamus appears to be single most important control area for the regulation of internal environment.

2-Brain-stem:

The brain-stem is the stalk of the brain, through it pass all the nerve fibers relaying signals of afferent input and efferent output between the spinal cord and higher brain centers. In addition, the brain stem gives rise to 12 pairs of cranial nerves, whose axons innervate the muscles and glands of the head and many organs in the thoracic and abdominal cavities.

Running through the entire brain-stem is a core of tissue called the reticular formation. Which is composed of small, highly branched neurons. These neurons receive and integrate information from many afferent pathways as well as from many other regions of the brain.

Mid-brain:

The smallest part of the brain tem, it is continuous with the pons below and the diencephalon above. The ventral surface is characterized by the large **cerebral peduncle**, lying laterally and carrying axons from the motor area of cerebrum to the brain-stem and to the cerebellum. The dorsal surface may be recognized by two pairs of protuberances, the superior and **inferior calculi. The superior collicular** neurons are concerned with the processing of visual information, and the inferior collicular neurons with auditory signals. Within the mud-brain, there exist centers active in the senses of hearing, vision and touch.

Pons:

Is continuous with the medulla and composed of fiber bundles that pass from the cerebrum to the spinal cord. Within the pons, many fibers from the fight and left sides of the brain cross over one another. Located within the pons are reflex centers that influence the rate of breathing and heartbeat.

Medulla:

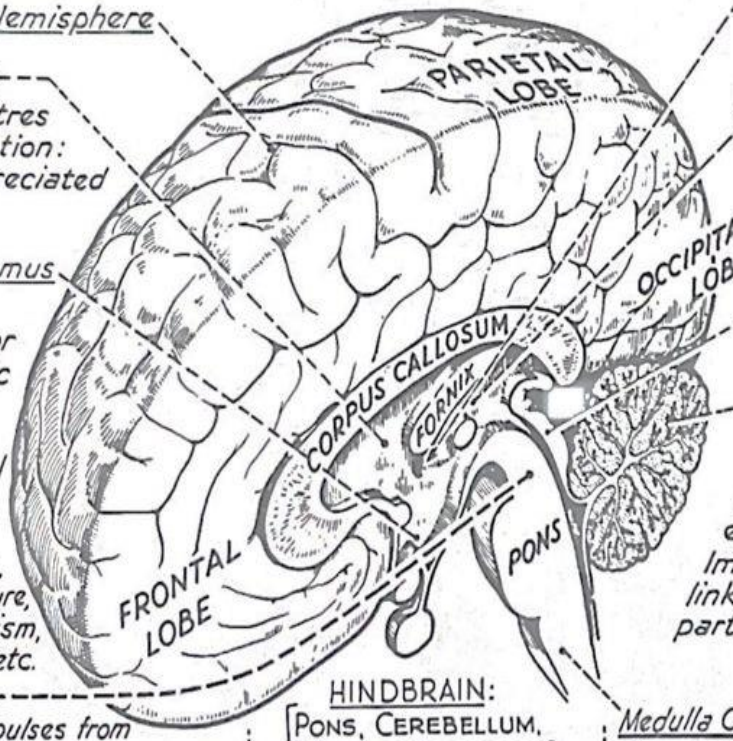
Is continuous with the spinal cord and contains the same fiber tracts. Several regulatory centers are present in the medulla, these centers help to control the rate of breathing, heartbeat, blood pressure, sweating, vomiting and the production of digestive juices in the stomach.

3-Cerebellum:

the cerebellum is involved with skeletal muscle functions, it help to maintain balance and to provide smooth, directed movements. The cerebellum is important in coordination voluntary muscular activities. It is similar to the cerebrum in having a central area of white matter surrounding by a covering of gray matter.

VERTICAL SECTION through BRAIN

This is a Vertical Section through the LONGITUDINAL FISSURE — a deep cleft which separates the two Cerebral Hemispheres. At the bottom of this cleft are tracts of nerve fibres which link up the different LOBES of each hemisphere and also link the two hemispheres with each other — the CORPUS CALLOSUM.



FOREBRAIN

Cerebral Hemisphere

Thalamus
- relay centres for sensation: pain appreciated here.

Hypothalamus
- contains centres for Autonomic Nervous System, e.g. Control of Heart, Blood pressure, Temperature, Metabolism, etc.

Opening of Lateral Ventricle

3rd Ventricle

Corpora Quadrigemina

Cerebellum
Centres concerned with balance and equilibrium. Important tracts link it with other parts of Brain and Spinal Cord.

MIDBRAIN
Receives impulses from Retina and Ear. Serves as a centre for Visual and Auditory Reflexes. In the Grey Matter are nerve cell bodies of III, IV Cranial nerves and the Red Nucleus which helps to control skilled muscular movements. The White Matter carries nerve fibres linking Red Nucleus with Cerebral Cortex, Thalamus, Cerebellum, Corpus Striatum and Spinal Cord. It also carries Ascending Sensory fibres in Lateral and Medial Lemnisci, and Descending Motor fibres on their way to Pons and Spinal Cord.

HINDBRAIN:
[PONS, CEREBELLUM, MEDULLA OBLONGATA]

Pons: Groups of Neurones form sensory nucleus of V and also nuclei of VI and VII Cranial nerves. Other nerve cells here relay impulses along their axons to Cerebellum and Cerebrum. Rubrospinal tract, Lateral and Medial Lemnisci pass through Pons and nerve fibres linking Cerebral Cortex with Medulla Oblongata and Spinal Cord.

Medulla Oblongata:
Groups of Neurones form Nuclei of VIII, IX, X, XI, XII Cranial nerves. Gracile and Cuneate Nuclei - second sensory neurones in cutaneous pathways. Tracts of Sensory fibres decussate and ascend to other side of Cerebral Cortex. Some fibres remain uncrossed. The larger part of each Motor pyramidal tract crosses and descends in other side of Spinal Cord.

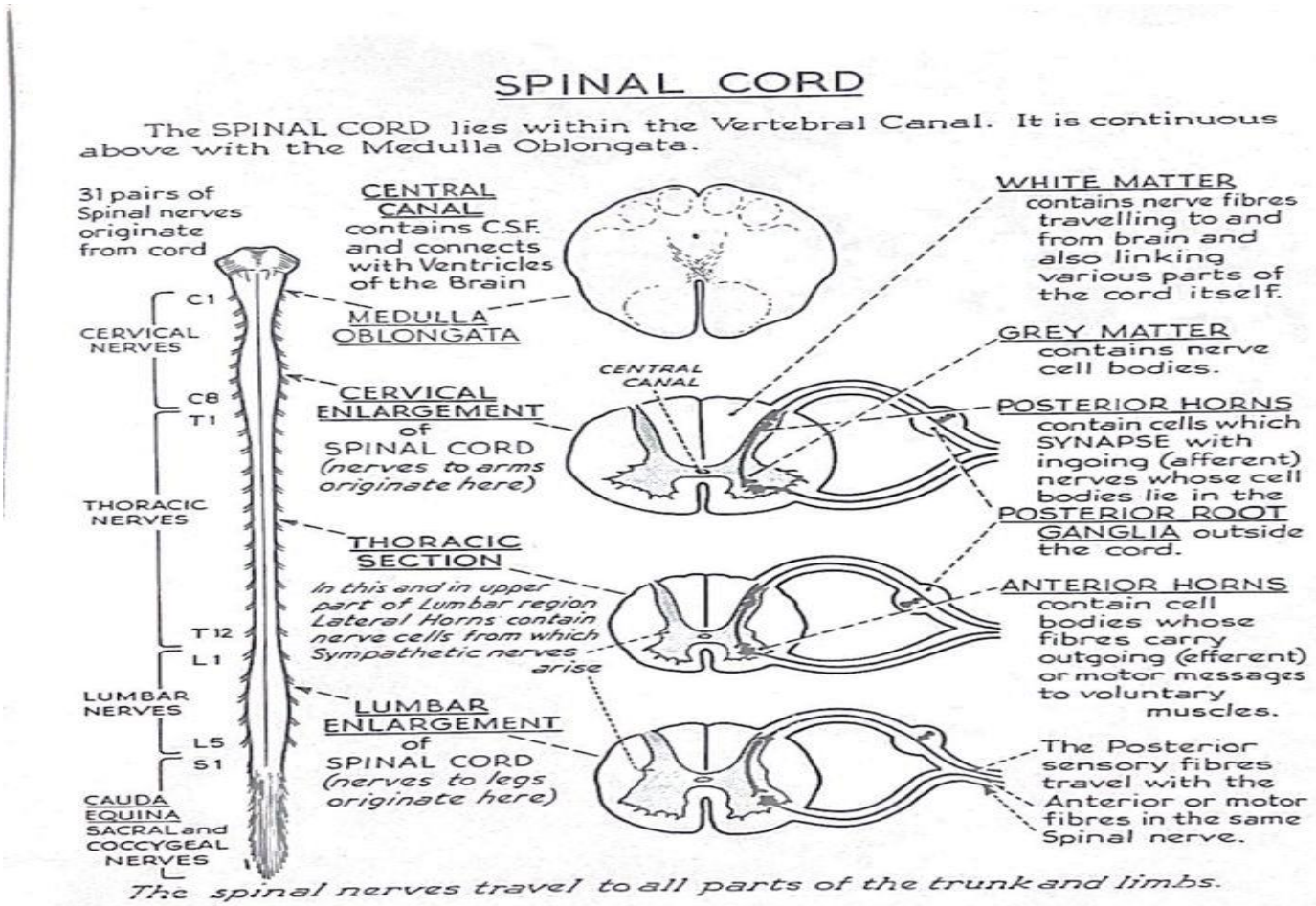
B- Spinal Cord Anatomy:

The spinal cord is connected to the brain and is about the diameter of a human finger. From the brain the spinal cord descends down the middle of the back nd is surrounding and protected by the bony vertebral column.

The spinal cord is surrounded by a clear fluid called Cerebral Spinal Fluid (CSF), that acts as a cushion to protect the delicate nerve tissues against damage from banging against the inside of the vertebrate.

The anatomy of the spinal cord itself, consists of millions of nerve fibers which transmit electrical information to and from the limbs, trunk and organs of the body, back to and from the brain. The nerves which exit the spinal cord in the upper section, the neck, control breathing and arms. The nerves which exit the spinal cord in the mid and lower section of the back, control the trunk and legs as well as bladder, bowel and sexual function. The nerves which carry information from the brain to muscles are called Motor Neurons. The nerves which carry information from the body back to the brain are called Sensory Neurons carry information to the brain about skin temperature, touch, pain and joint position.

The brain and spinal cord are referred to as the Central Nervous System, while the nerves connected the spinal cord to the body are referred to as the Peripheral Nervous System.



PERIPHERAL NERVOUS SYSTEM

Divisions of Peripheral nervous system
I. Afferent division II. Efferent division a. Somatic nervous system b. Autonomic nervous system 1. Sympathetic division 2. Para-sympathetic division

Afferent division:

Afferent neurons convey information from receptors in the periphery to the central nervous system. The cells bodies of afferent neurons are outside of the brain or spinal cord in structure called ganglia. From the region of the cell body, one long process (the peripheral process) extends away from the ganglion out to the receptors; commonly, the process branches several times as it nears its destination, each branch containing or innervating one receptor. A second process (the central process) passes from the body into the central nervous system, where it branches; these branches terminate in synapses on other neurons.

Efferent division:

The efferent division is more complicated than the afferent, being subdivided into a somatic nervous system and an autonomic nervous system. These terms are somewhat unfortunate because they conjure up additional "nervous system" distinct from the central and peripheral nervous systems. Keep in mind that the terms refer simply to the efferent division of the peripheral nervous system.

Although separating these two divisions is justified by many anatomical and physiological differences, the simplest distinction between the two is that the somatic nerve fibers innervate skeletal muscles, whereas the autonomic nerve fibers innervate smooth and cardiac muscle and glands. Outer differences are listed in Table 2.

Table (2)

Differences between somatic and autonomic nervous system	
Somatic nervous system	**Autonomic nervous system**
Consists of a single neuron between the central nervous system and the effector organ	Has a two-neuron chain (connected by a synapse) between the central nervous system and the effector
Innervates skeletal muscles	Innervates smooth and cardiac muscles or glands
Always leads to excitation of the muscle	Can lead to excitation or inhibition of the effector cells

SOMATIC NERVOUS SYSTEM

The somatic division of the peripheral nervous system is made up of all the fibers going the central nervous system to skeletal muscle cells. The cell bodies of these neurons are located in groups in the brain or spinal cord; their large-diameter, myelinated axons leave the central nervous system and pass directly (i.e., without any synapses) to skeletal muscle cells. The neurotransmitter substance released by these neurons is acetylcholine. Because activity in the somatic efferent neurons leads t contraction of the innervated skeletal muscle cells, these neurons are often called motor neurons. Excitation of motor neurons only leads to the contraction of skeletal muscle cells; there are no inhibitory somatic neurons.

Cranial nerves:

There are twelve pairs of cranial nerves. Two of these pairs arise from neurone cell bodies located in the forebrain and ten pairs arise from the midbrain and hindbrain. The cranial nerves are designated by Roman numerals and by names. The Roman numerals refer to the order in which the nerves are positioned from the front of the brain to the back. The names indicate structures innervated by these nerves (e.g., facial) or the principal function of the nerves (e.g., oculomotor).

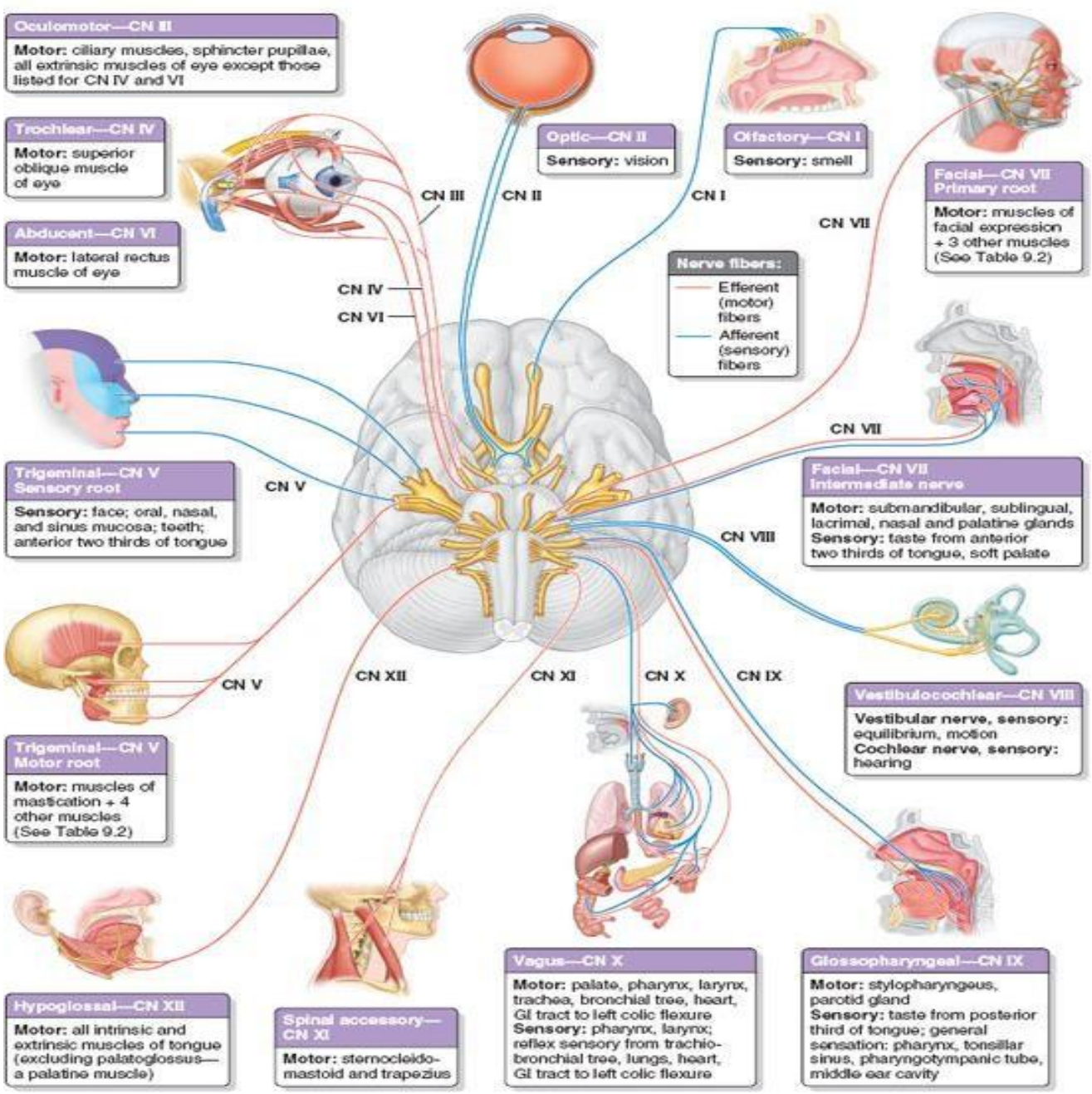
Most cranial nerves are classified as mixed nerves. This term indicates that the nerve contains both sensory and motor fibers. Those cranial nerves associated with the special senses (e.g., olfactory; optic), however, consist of sensory fibers only. The cell bodies of these sensory neurones are not located in the brain, but instead are found in ganglia near the sensory organ.

Crinal nerves are.

Olfactory Optic- Oculomotor
Trochlear Abducens Facial-
Vestibulocochlear Glossopharyngeal
Vagus Accessory Hypoglossal

Cranial Nerves

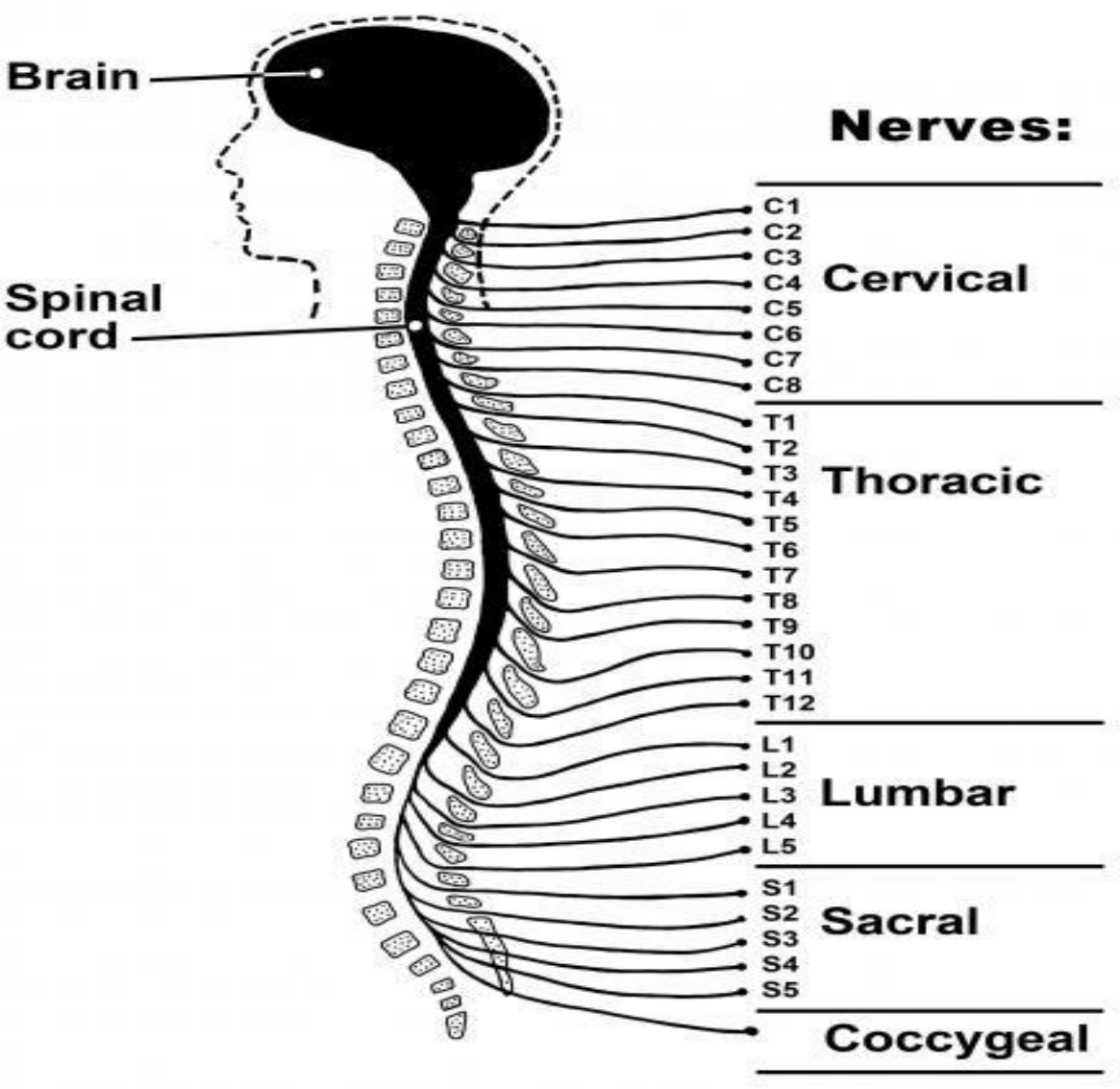
Attached to the brain are 12 pairs of cranial nerves. Three of them contain sensory nerve fibers and conduct impulses into the brain. Five contain motor nerve fibers and conduct impulses from the brain out to various body regions. The remaining four are mixed nerves, composed of both sensory and motor fibers.



Spinal nerves:

There are thirty one pairs of spinal nerves. These nerves are grouped into eight cervical, twelve thoracic, five lumbar, five sacral and one coccygeal according to the region of the vertebral column from which they arise.

Each spinal nerve is a mixed nerve composed of sensory and motor fibers, these fibers are packaged together in the nerve, but separate near the attachment of the nerve to the spinal cord. This produces two "roots" to each nerve. The dorsal root is composed of sensory fibers, and the ventral root is composed of motor fibers. The dorsal root contains an enlargement called the dorsal root ganglion, where the cell bodies of the sensory neurons are located, thus the dorsal root, carries information into the spinal cord from peripheral receptors, and the ventral root, carries signals out.



REFLEXES

A reflex is an involuntary, unlearned response to a stimulus. It is common knowledge that application of many kinds of stimulus to different parts of the body produces an involuntary movement. Many reflexes regulating the internal environment occur without any conscious awareness. Examples of such basic reflexes would be pulling one's hand away from a hot object or shutting one's eyes as an object rapidly approaches the face. However, there are also many responses which appear to be automatic and stereotyped but which actually are the result of learning and practice. For example, an experienced driver performs many. Complicated acts in operating a car, to the driver these motions are, in large part, automatic, stereotyped, and unpremeditated, but they occur only because a great deal of conscious effort was spent to learn them. We shall refer to such reflexes as learned or acquired.

The reflex Arc

The structural background of reflex activity is chain of sensory, connector and motor neurons, which form the pathway of the nerve impulse that travel from a receptor to an effector organ during the performance of any reflex. The pathway is known as a reflex arc. There must be at least two neurons in a reflex arc, but usually there are more.

In a somatic spinal reflex arc, three neurons may be involved:

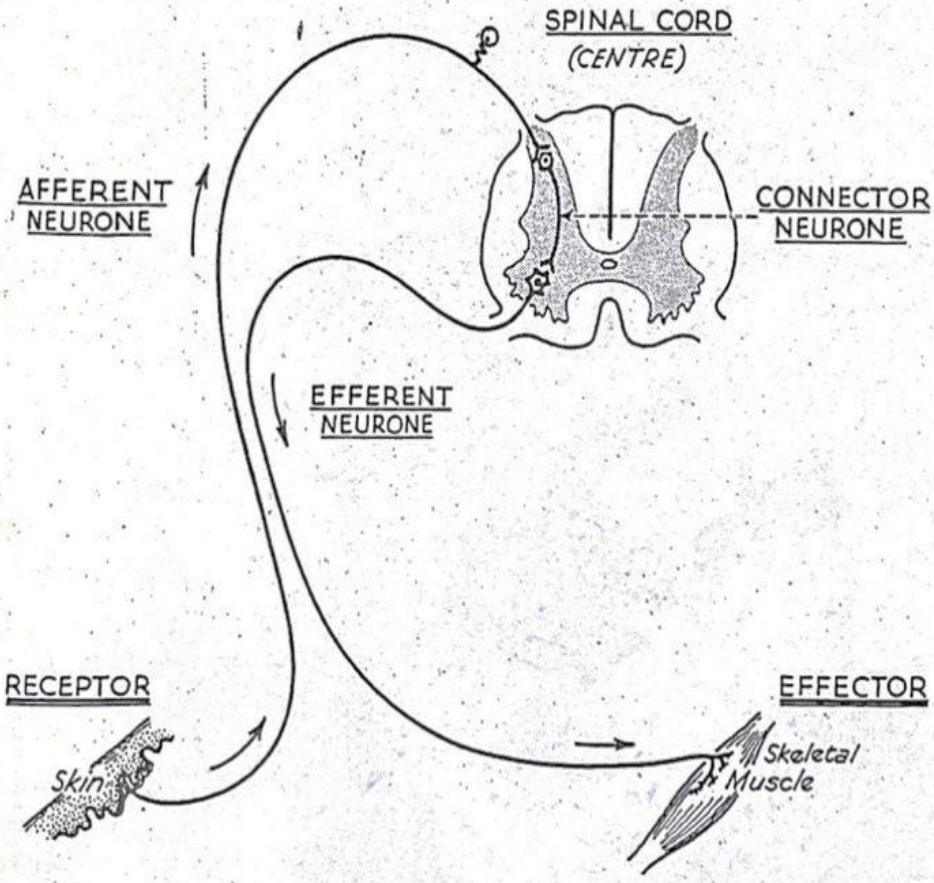
1- The afferent or receptor neuron with its cell body in the dorsal root ganglion.

2- A connector neuron in the dorsal horn of grey matter which by means of its axons transmits the impulse to the ventral horn.

3- The ventral horn cell and its axon-the excitor neuron which transmits the efferent impulses to skeletal muscle.

SPINAL REFLEXES

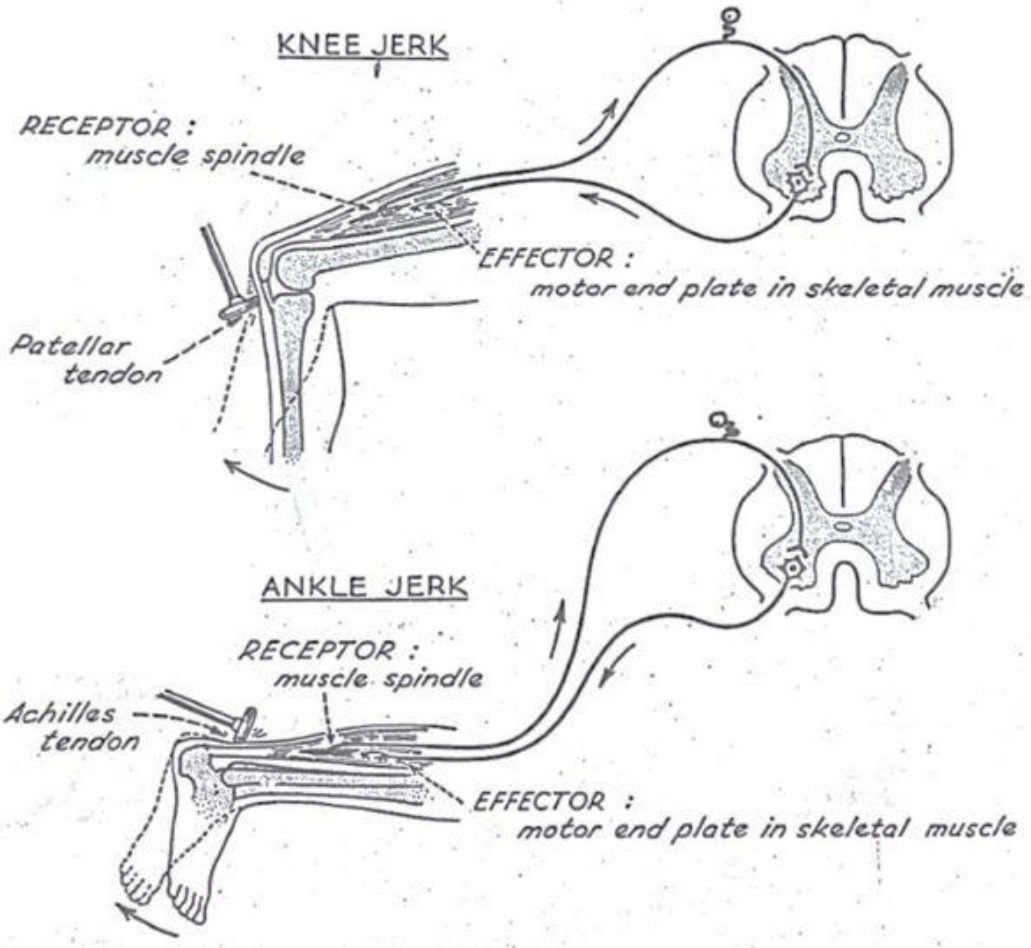
In most REFLEX ARCS in man AFFERENT and EFFERENT NEURONES are linked by at least 1 CONNECTOR NEURONE



A chain of many connector neurones is frequently found.

STRETCH REFLEXES

In man a very few REFLEX ARCS involve 2 NEURONES only. Two examples elicited by doctors when testing the Nervous System are:—



When the tendon is sharply tapped the muscle is stretched. (N.B. The stimulus is by stretch of the muscle spindle.) Nerve messages pass into the spinal cord — and out to the muscle which then contracts.

THE NERVE IMPULSE

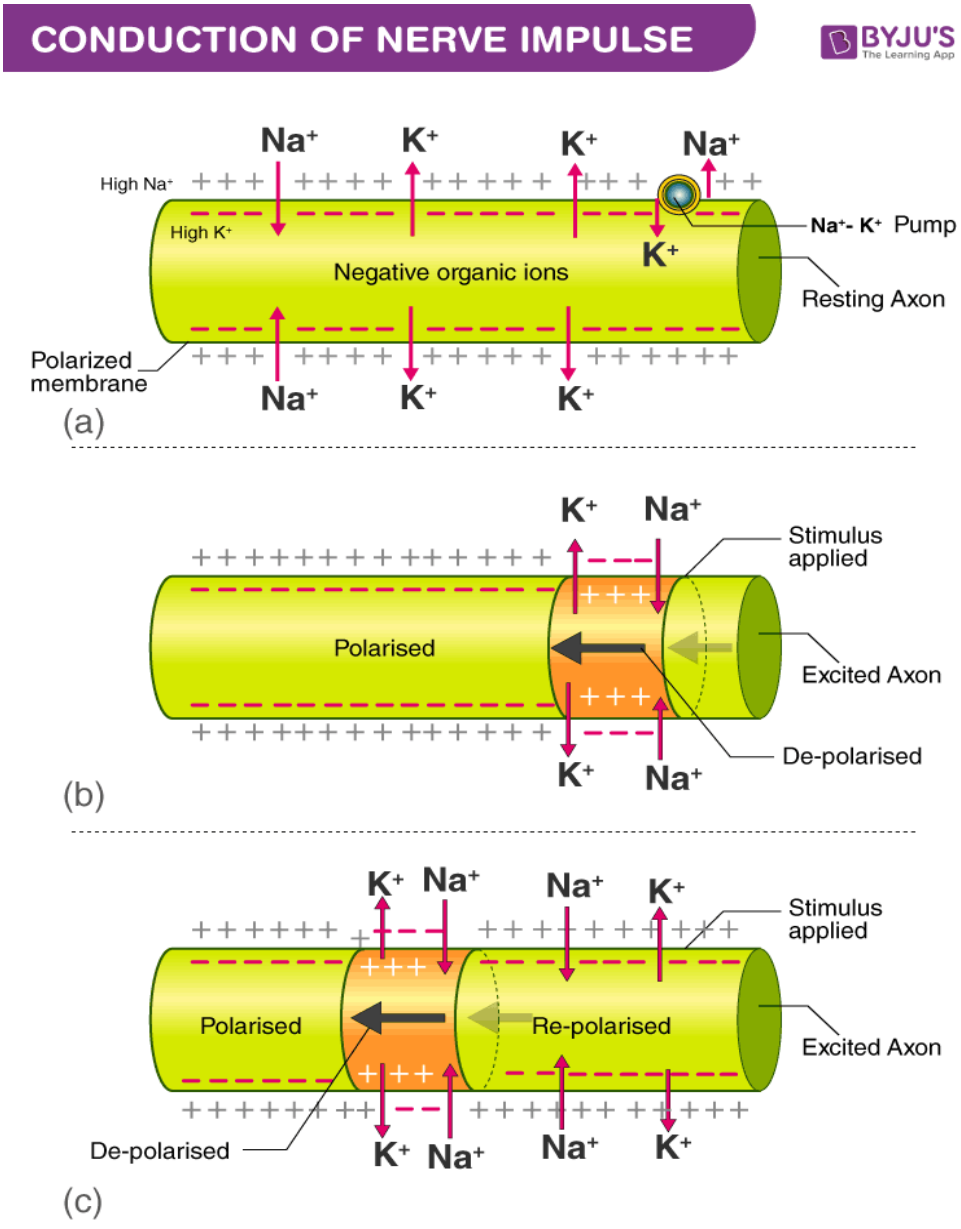
The main function of a neuron is to transmit information rapidly from one part of the body to another. It does so in the form of a nerve impulse. The nerve impulse can be described both as an electrical and chemical event, and involves the selective permeability of the cell membrane surrounding the neuron.

A resting neuron (on that is not conducting an impulse) actively transports positively charged sodium ions to the outside of the cell, while allowing positively charged potassium ions to pass into the cel. Negatively charged ions are not free to move through the membrane, and the number of sodium ins transported out is greater than the number of potassium ions that pass into the cell. Cell membranes tend to be relatively permeable to potassium ions and since the intracellular K^+ ion concentration is greater than the extracellular level, there is a great strong tendency for K^+ to leak out of cells. Also the K ions are exposed to an attraction towards the internal negative charge. The result is a difference in charge on the two sides of the cell membrane. This difference in electrical charge is referred to as the membrane potential, (or potassium diffusion potential) and the cell is said to be polarized. Thus, when in the resting state, the exterior of the neuron is positively charged with respect to the interior.

A nerve impulse may originate at any point the nerve cell that is properly stimulated; however under normal circumstances, the impulse , originates on the ends of the dendrites and passes to the ends of the axon. Once stimulated the membrane of the axon suddenly becomes permeable to the sodium ions that have become concentrated on the outside and outside and sodium rapidly diffuses into the cell. This sudden flow of positive ions into the cell temporarily reverses the polarity of the membrane, and the cell's interior momentarily becomes positively charged with respect to the exterior, so the action potential is largely a Sodium diffusion potential. The change in membrane permeability that allowed sodium to enter the cell now permits positively charged potassium ions to diffuse out. Almost enough potassium passes out to equal the number of sodium ions that entered the cell, thereby almost reestablishing the original resting membrane polarity. The cell now returns to pumping sodium out of the cell while allowing potassium to

return back into cytoplasm. All of this occurs in less than five thousandths of a second.

If the event just described occurred only at one spot on the neuron, the impulse would end right where it began. Instead, the change of the polarity at one the membrane stimulates adjacent parts, initiating the same sequence of ions flow and depolarization. As each new section of membrane becomes depolarized, it in turn stimulates adjacent areas, and so a wave sweeps along the axon. This wave is the nerve impulse.



Generally, as soon as a portion of the membrane has been restored a polarized state, it is capable of transmitting another impulse. One advantage of nervous system over a hormonal one for communication is the speed at which a nervous system can deliver messages. The circulatory system may take seconds to deliver a hormone to different parts of the body, but nerve impulses can be delivered in small fractions of a second. Even in the slowest neurons, an impulse travels at about one half meter per second and in the fastest neurons impulses can move at rates up to 100 meters per second.

Differences in speed of transmission between different neurons depend on the diameter and structure of the axon. Those that transmit impulses most rapidly are large and possess a myelin sheath. The sheath is impermeable to ions except at very thin areas that occur at intervals along the axon. Apparently the high rate of movement along an axon of this type is possible because the impulse is able to "jump" from one thin region to the next, traversing the length of the cell in a fraction of the time required in a nonmyelinated cell of the same length.

A nerve impulse is a signal that travels along a neurone as sodium and potassium ions pass through the membrane in opposite directions this impulse can travel from the central nervous system to the tip of your fingers in less than 1/100 of a second.

THE SYNAPSE

A synapse is the functional connection between a neuron and a second cell. There is no cytoplasmic continuity between them. In the CNS, this other cell is also a neuron. In the CNS the other cell may be a neuron or an *effector* cell within a muscle or a gland. Although the physiological of neuron-neuron synapses and neuron-muscle is similar, the latter synapses are often called *myoneural, or neuromuscular, junctions*.

Neuron-neuron synapses usually involve a connection between the axon of one neuron and the dendrites, cell body, or axon of a second neuron. These are called, respectively, *axodendritic, axosomayic* and *axoaxonic synapses* . in almost all synapses, transmission is in one direction only from the axon of the first (or presynaptic) cell to the

second (or postsynaptic) cell. Dendrodendritic synapses do not fit this classic pattern; in these synapses, two dendrites from different neurons make reciprocal innervations some of these synapses conduct in one direction and others conduct in the opposite direction.

Synaptic transmission might be chemical that the presynaptic nerve endings might be release chemical called *neurotransmitters* that stimulated action potentials in the postsynaptic cells.

More recent evidence, has shown that electrical synapses do exist in the nervous system (through they are the exception), within smooth muscles, and between cardiac cells in the heart.

Types of synapses

Electrical Synapses: Gap Junctions

In order for two cells to be electrical couples, hey must be approximately equal in *size* and they must be joined by areas of contact with low electrical resistance.

Adjacent cells that are electrical couples are together by *gap junctions*. In gap junctions, the membranes of the two cells are separated by only 2 nanometers (1 nanometer equals 10^{-9} meter).

Gap junction are present in cardiac muscles and smooth muscles, where they allow excitation and rhythmic contraction of large masses of muscle cells. Gap junctions have also been observed in various regions of the brain. Although their functional significance in the brain is unknown, it has been speculated that they may allow a two-way transmission of impulses(in contrast to chemical synapses, which are always one-way). Gap junctions have also been observed between neuroglia cells, which do not produce electrical impulses. Many embryonic tissues have gap junctions, and these gap junctions disappear as the tissue becomes more specialized.

Chemical Synapses

Transmission across the majority of synapses in the nervous system is one-way and occurs through the release of chemical neurotransmitters from presynaptic axon endings, which are called chemical terminal boutons because of their swollen appearance, are separated from the

postsynaptic cell a synaptic cleft so narrow that it can be seen clearly only with an electric microscope.

Neurotransmitter molecules within the presynaptic neuron endings are contains within many small, membrane enclosed synaptic vesicles. In order for the neurotransmitter within these vesicles to be released into the synaptic cleft, the vesicle membrane must fuse with the axon membrane in the process of *exocytosis*. The number of vesicles that undergo exocytosis is directly related to the frequency of action potentials produced at the presynaptic axon ending, therefore, when stimulates to the presynaptic axon is increased, more vesicles will undergo exocytosis and release their neurotransmitters, so that the postsynaptic cell will be more greatly affected.

Action potentials in the terminal bouyon of the presynaptic axon cause the opening of voltage-regulated Ca^{++} channels. There is thus a sudden, transient inflow of Ca^{++} into the presynaptic endings. Ca^{++} activates a regulatory protein within the cytoplasm called calmodulin, which inturn activates an enzyme called protein kinase. This enzyme phosphorylates (adds a phosphate group to) specific proteins known as synapsins in the membrane of the synaptic vesicle. This permits the vesicle to undergo exocytosis and release its content of neurotransmitter molecules. Regulation by Ca^{++} , calmodulin and protein kinase is also involved in the action of some hormones.

Once the neurotransmitter molecules have been released from the presynaptic axon terminals, they diffuse rapidly across the synaptic cleft and reach the membrane of the postsynaptic cell. The neurotransmitters then bind to specific receptor proteins that are part of the postsynaptic membrane. Binding of the neurotransmitter to its receptor protein causes ion channels to open in the postsynaptic membrane. The gates that regulate these channels, therefore, can called chemically regulated gates because they open in response to chemical changes in the postsynaptic cell membrane.

Mechanism of transmission of impulse through Synapses

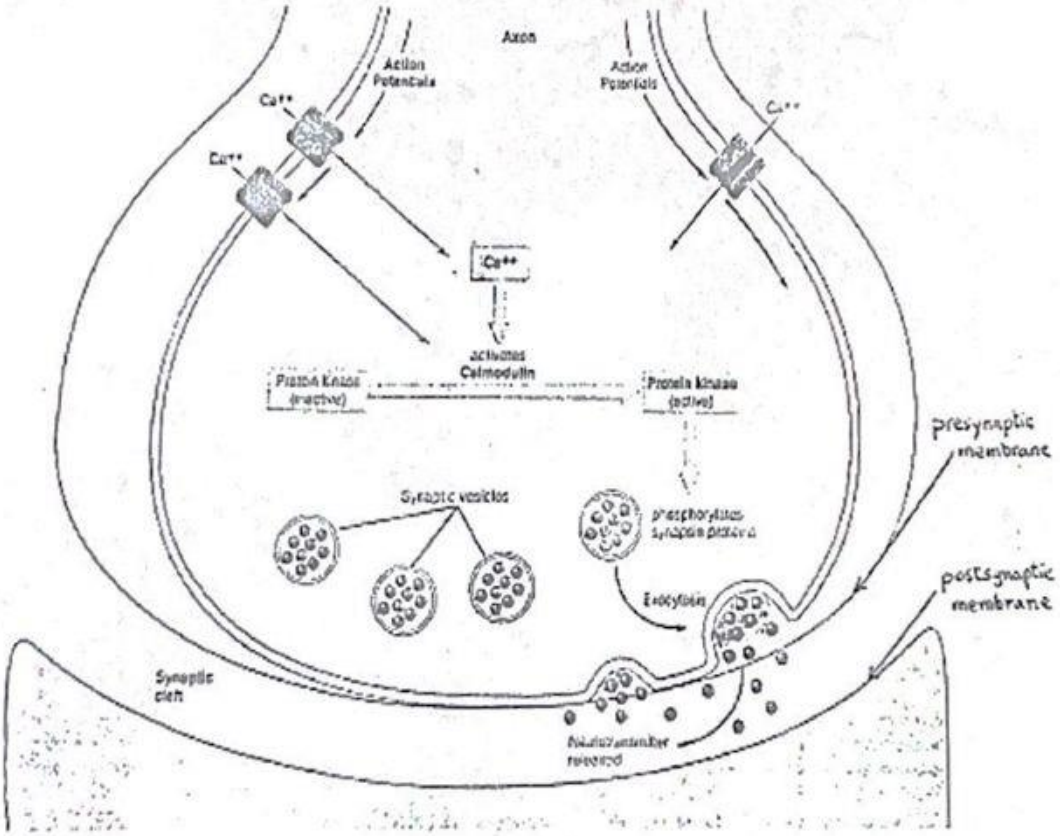
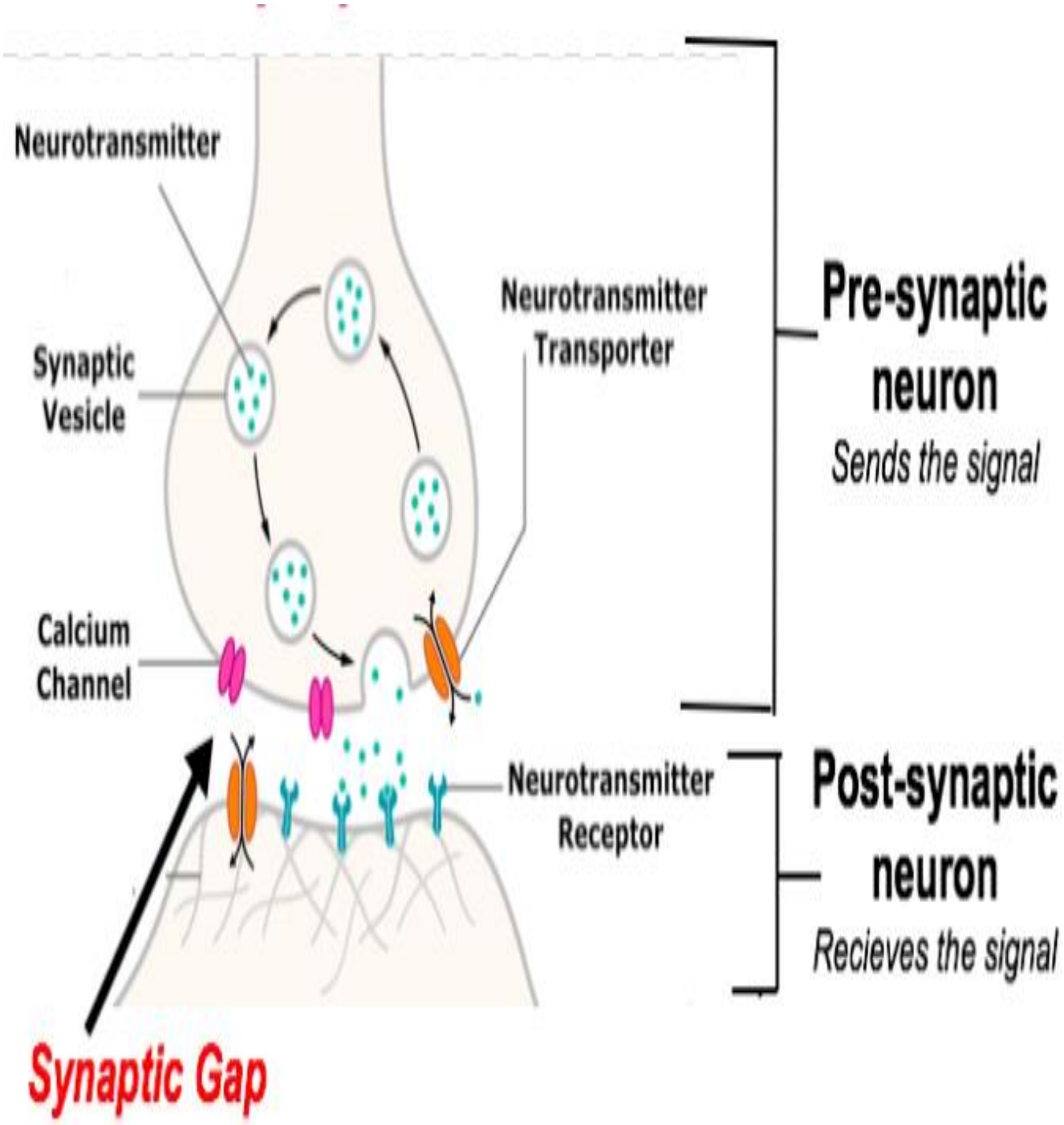


Figure 8

Action potentials at the axon terminals open Ca^{++} channels. The inward diffusion of Ca^{++} activates the protein calmodulin, which in turn activates the enzyme protein kinase. Activity of the enzyme results in the release of neurotransmitter molecules from the terminal button of the axon.

Structure of Synapses



Types of synapse according to its functions

1- Postsynaptic excitation:

By the arrival of a nerve impulse to the nerve terminal and entery of Ca++ ions, the mediator produced in the nerve endings is freed from its bound state and secreted into the synaptic cleft. Since the latter is very narrow the mediator quickly (within about 0.5 millisecond) diffuses to the postsynaptic membrane and interacts with its receptors. That results in a considerable increase in the permeability of the postsynaptic membrane to sodium and potassium ions, which is followed by its depolarization and the appearance of what is called the excitatory postsynaptic potential. As soon as this potential has reached the critical value a wave of excitation (an action potential or spike) arises in the cell. Since the membrane of the initial segment of the axon has the lowest critical level of depolarization, the action potential is generated first in that part of the neurone and spreads from there both to the cell body and along the axon.

As regards certain excitatory synapses in the brain and spinal cord is has been established that the mediator in them is acetylcholine. It is also known that the level of certain other highly active compounds (dopamine, noradrenaline, serotonin) which are possibly also mediators, is increased in the tissues of the brain and spinal cord during intense excitation.

2- Postsynaptic inhibition:

Is begins by the arrival of a nerve impulse to the nerve terminals, then opening of calcium channels and entery of Ca2+ ions. The transmitter present in the synaptic vesicle is released into the extracellular fluid when a vesicle fuses with the membrane of the nerve terminal. The transmitter

Diffuses across the synaptic gap to the post synaptic membrane where it combines with specialized receptors. The combination of the neurotransmitter with its receptors results in hyperpolarization of the postsynaptic membrane (the inside of the membrane becomes more

negative than it is at rest) so the response is inhibitory and the local hyperpolarization is an inhibitory postsynaptic potential(IPSP). Neurons

releasing neurotransmitter substances that cause IPSPS are inhibitory neurons. The IPSP is the result of an increase in the permeability of the cell membrane to chloride (Cl^-) or potassium (K^+) ions.

Because (Cl^-) ions are more concentrated outside the cell than inside, when the permeability of the membrane of Cl^- ions increases, they diffuse into the cell, causing the inside of the cell to become more negatively and resulting in hyperpolarization. The concentration of K^+ ions is grater inside the cell than outside, and increased permeability of the membrane of K^+ outside the cell. Consequently, the outside of the cell becomes more positive than inside, resulting in hyperpolarization.

Transmitter substances (Mediators):

The terminal region of each branch of an axon contains a chemical transmitter substance that it secretes into synapse whenever an impulse arrives. The chemical diffuses across the synapse to the membrane of the next neuron. The effect of the transmitter substance is to act as a stimulate to the next neuron by the permeability of its membrane to become permeable to sodium ions.

Several different compounds have been identified as transmitter substances. Acetylcholine, norepinephrine and serotonin are all examples of compounds that act as transmitter substances in different parts of the nervous system, with the latter acting in certain portions of the brain. Once a transmitter substance has been released into a synapse and performs its function on the opposing membrane. It must be removes from the region so that it will not interfere with transmission of subsequent impulses.

Acetylcholine:

The mediator function of acetylcholine provides a good example of chemical mediation of synaptic activity. Neuron that release acetylcholine are known as cholinergic neurons.

The arrival of an impulse at a synaptic knob increases the Ca^{2+} permeability of the membrane, and the resultant Ca^{2+} influx causes liberation of acetylcholine into the synaptic cleft by the process of exocytosis. The transmitter crosses the cleft and at these synaptic junctions where acetylcholine is an excitatory mediator, it acts on receptors on the membrane of the postsynaptic cell to increase the permeability of the membrane to Na^+.

Cholinesterase:

Acetylcholine must be rapidly removed from the synapse if repolarization is to occur. Some is taken up again by the presynaptic terminals, but most is hydrolyzed by a process catalyzed by the enzyme acetyl cholinesterase (AchE) this is also called true or specific cholinesterase. It is present in high concentrations in the cell membranes at nerve terminals that are cholinergic. There are a variety of esterases in body. One found in plasma is capable of hydrolyzing acetylcholine but has different properties from acetyl cholinesterase. It is therefore called pseudo cholinesterase or nonspecific cholinesterase.

Acetylcholine synthesis:

Synthesis of acetylcholine involves the reaction of choline with acetate. There is an active uptake of choline into cholinergic neurons. The acetate is activated by the combination of acetate groups with reduced coenzyme A. the reaction between active acetate (acetyl-coenzyme A) and choline is catalyzed by the enzyme choline acetyltransferase. This enzyme is found in high concentration in the cytoplasm of cholinergic nerve endings.

Other chemical Mediators:

Norepinephrine, dopamine, epinephrine and 5-hydroxy-tryptamine (serotonin) are among the mediators found in the CNS. Neurons that secrete norepinephrine or epinephrine are called adrenergic neurons. Histamine, peptides such as "substance P" and other agents may also be mediators in the rain.

Interest in the action of amino acids upon the mammalian central nervous system is closely linked with the possible role of some these compounds as central transmitter substances. It has been shown that glutamic acid has a potent excitatory effect on invertebrate and neurons. Gamma-aminobutyric acid (GABA) has been proved to be the mediator for presynaptic inhibition in the spinal cord and an inhibitory mediator in the brain and in the retina of mammals. Glycine in the mediator responsible for direct inhibition in the spinal cord.

AUTONOMIC NERVOUS SYSTEM

The autonomic nervous system innervates organs whose functions are not usually under voluntary control. The effectors that responds to autonomic regulation include cardiac muscle (the heart), smooth(vesicle) muscles, and glands. Anatomical and physiological differences within the autonomic nervous system are the basis for its further subdivision into sympathetic and parasympathetic components. The cell bodies of the first neurons in the two subdivisions are located in different areas of the central nervous system and their fibers ,leave at different levels. The synaptic fibers from the thoracic and lumbar regions of the spinal cord, (from T_1 to L_2) and the parasympathetic from the brain (specially, the mid brain, medulla oblongata and pons) and the sacral portion the spinal cord. Thus, the sympathetic division is also called the thoracolumbar division, and the parasympathetic the craniosacral division.

The organization of the autonomic nervous system differs from the somatic division as all final motor neurons lie completely outside the CNS. The cell bodies of the peripheral neurons are grouped together to form ganglia. The efferent fibers passing from the CNS to the ganglia, the preganglionic fibers, release the neurotransmitter Ac. The final motor neurons from the ganglia to the tissues, the postganglionic fibers, and fibers form visceral sensory receptors run together as visceral nerves.

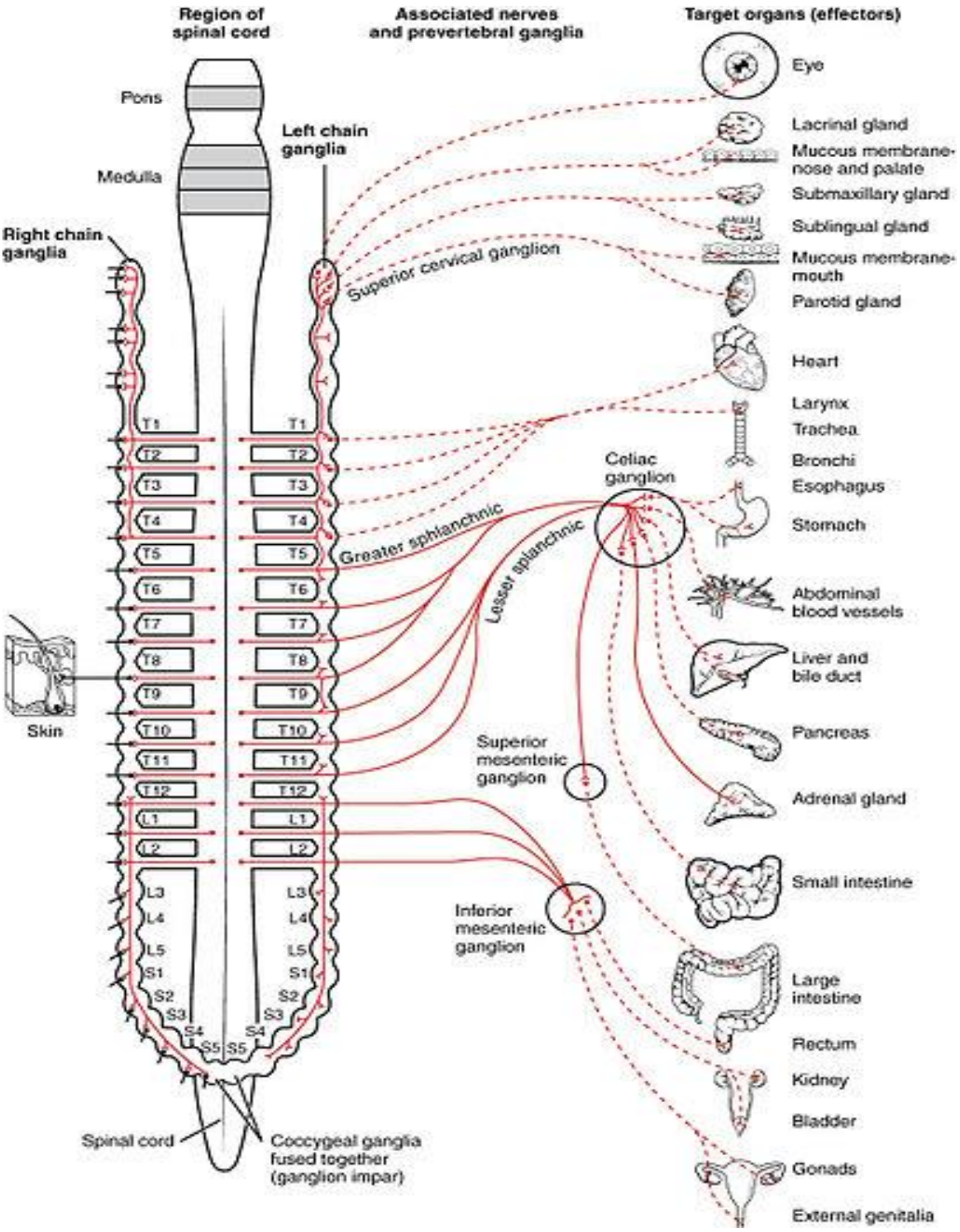
Sympathetic system

All preganglionic sympathetic nerves have their cell bodies in the thoracic and upper lumbar segments (T_1-L_2). The axons, along with somatic motor fibers, pass out of the spinal in the ventral roots. On leaving the spinal column, the preganglionic fibers separate from the somatic nerves to form the which rami communicants and join a distinct group of sympathetic ganglia, the vertebral (paravertebral or chain) ganglia. These ganglia are segmentally arranged and lie along each side of the spinal column. The preganglionic fibers either:

(a) Synapse with postganglionic neurons is one or more of the vertebral ganglia, or
(b) Leave the vertebral ganglia in visceral nerves and pass to paravertebral ganglia in the abdomen or to the adrenal medulla.

Many of the postganglionic fibers from vertebral ganglia leave the ganglia as the grey rami communication and join the spinal nerves that pass to peripheral tissue, join visceral nerves to postganglionic organs. Most of these postganglionic fibers release the neurotransmitter noradrenaline (norepinephrine) and are referred to as adrenergic fibers. The adrenal medulla can be thought of as modified ganglia that release the hormone adrenaline (epinephrine), and also some noradrenaline, into the bloodstream rather than directly onto effector cells. Small groups of sympathetic nerves that do not release noradrenaline innervate the blood vessels of muscles, sweat glands and their follicles in the skin, and release acetylcholine. The distribution of the postganglionic sympathetic nerves is not necessarily the same as the somatic motor nerves from the same segment and there is a lot of overlap between adjacent outflows. In brief, and very approximately, the T_1 outflow passes to the head, T_2 to the neck, T_3-T_6 to the thorax, T_7-T_{11} to the abdomen and T_{12}-L_2 to the legs.

Sympathetic System



Parasympathetic system:

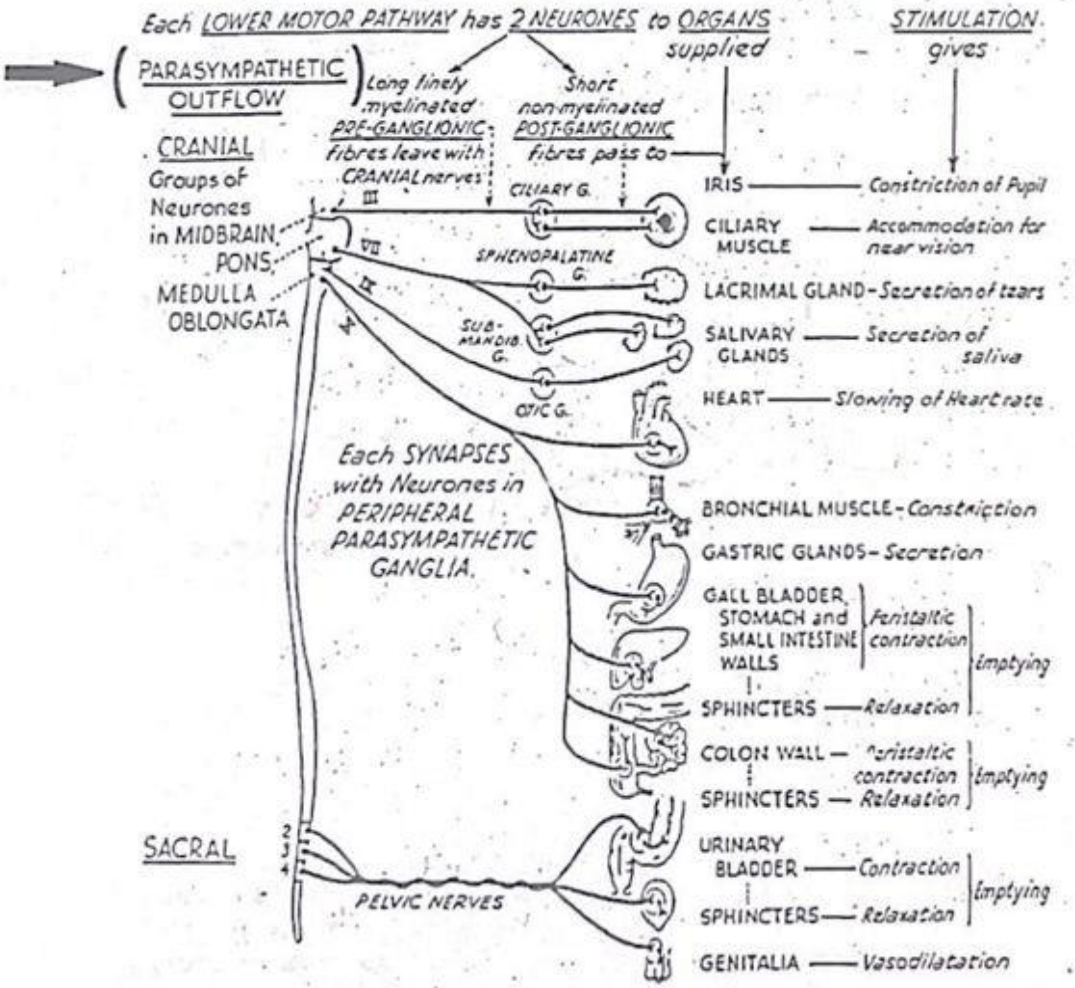
The preganglionic nerves of the parasympathetic system come from both the brain-stem and sacral cord (S_2-S_4); the axons from the brain stem leave in cranial nerves III, VII, IX and X and the sacral axons leave in the ventral roots. There are not vertebral or paravertebral ganglia in this system; instead all ganglia are found adjacent to or within the effector organ. The postganglionic fibers from parasympathetic ganglia are relatively short and nearly all release acetylcholine as a neurotransmitter. In most cases the distribution of the parasympathetic outflow is more restricted than that of the sympathetic system. Thus cranial nerve III supplies the smooth muscle of the eye (ciliary muscle and pupillary constrictor muscle), VII the lacrimal and sub maxillary glands, and IX the parotid gland. The major and most widely distributed parasympathetic outflow travels in cranial nerve X, the vages.

Approximately 70% of all parasympathetic preganglionic fibers leave the CNS in this nerve and supply all viscera in the thorax and most of all viscera in the abdomen. The sacral parasympathetic outflow supplies the lower colon, rectum, bladder, the lower part of the ureters and the external genitalia.

parasympathetic system

The Autonomic Nervous System is concerned with maintaining a Stable Internal Environment. It governs functions which are normally carried out below the level of consciousness.

It has 2 separate parts - PARASYMPATHETIC and SYMPATHETIC. Both have their Highest Centres in the Brain.



General stimulation of the Parasympathetic promotes vegetative functions of the body. Stimulation of the Parasympathetic and inhibition of Sympathetic have the same overall effects.

Functions of Autonomic Systems

A-Sympathetic system:

1-In general, the sympathetic system preserves homeostasis. However, the sympathetic nervous system can be active under normal conditions, and some of the postganglionic fibers discharge topically "at rest".

2-In emergency situations (intense muscular exercise, stress. Fear, cold, fatigue, hemorrhage, etc.) there is a generalized discharge of the sympathetic system. This includes not only an increase in the firing frequency of fibers discharging topically but nit also activating of sympathetic fibers that are silent at rest (fibers directed to sweat glands, pilomotor muscles and the adrenal medulla, as well as vasodilator fibers to muscle).

a-During strenuous muscular exercise, sympathetic activity is directed toward supplying adequate energy to the working muscles and removing waste products from them. This is accomplished by

(1) Activation of vasodilator fibers to muscles and vasoconstrictor fibers to other areas (principally splanchnic), which shift an important part of the cardiac output to the active areas

(2) An increase in cardiac output by augmented venous return (sympathetic effects in veins and arterioles), a rise in cardiac frequency and augmentation of myocardial contractility, (sympathetic effects on the pacemaker and the myocardium).

(3) The dilator fibers to the bronchi favor oxygenation.

(4) Activation of the adrenal medulla leads to release of epinephrine and norepinephrine into the circulation. The effects of both adrenal catechol amines are mainly metabolic in these circumstances and effectors organs are fully activated. In the liver glycogenolysis is increased by epinephrine and the blood sugar level rises; in muscle, glycolysis is increased and the lactic acid level rises. In adipose tissues there is a more rapid hydrolysis of triglycerides and an increase in the rate of mobilization of free fatty acids. Both mechanisms lead to an increased supply of the metabolic fuels-carbohydrates and free fatty acids necessary for muscular activity.

(5) Activity of the sympathetic fibers to sweat glands and an increase in blood flow to the skin, allow the dissipation of heat engendered muscle by exercise.

(6) Other functions, temporarily of minor importance, are inhibited e.g. intestinal motility is inhibited by the activity of sympathetic fibers innervating the intestine.

What has been described is the general pattern of sympathetic activation. However; some differences are seen in different emergency situations.

b-For instance, expose to cold leads to muscular contractions (shivering), and the heat produced by this mechanism and by adrenal medullary activity is preserved through intense cutaneous vasoconstriction and piloerection.

c- In hemorrhage, the bold flow through the skin is reduced by stimulated of sympathetic vasomotor fibers.

3-It must be stressed that one of the most important functions of the sympathetic system is the regulation of vasomotor tone; indeed, this is accomplished almost exclusively by means of the sympathetic nerves. Activity of these nerves produced contraction of arteriolar smooth muscles, so that the arterioles are constricted and the blood pressure rises. Another important sympathetic effect on the cardiovascular system is that produced by epinephrine transported via the blood or by norepinephrine released from sympathetic terminals innervating the heart. Both substances increase the frequency of the heartbeat and the strength of contraction of the heart muscle.

Most of the sympathetic fibers provoked vasoconstriction, but some of them induced the possible effect in some tissues. Classic in this respect is the effect of sympathetic stimulation on the blood supply to muscles (both cardiac and skeletal); sympathetic stimulation may evoke vasodilatation and consequently an increase in blood flow.

B-Parasympathetic system

The parasympathetic nervous system has specific effects according to the kind of visceral effector that is subjected to its actions. In the head, parasympathetic supply is provided by cranial III, VII and IX, part of the supply is directed to the eye, where these fibers contract the sphincter

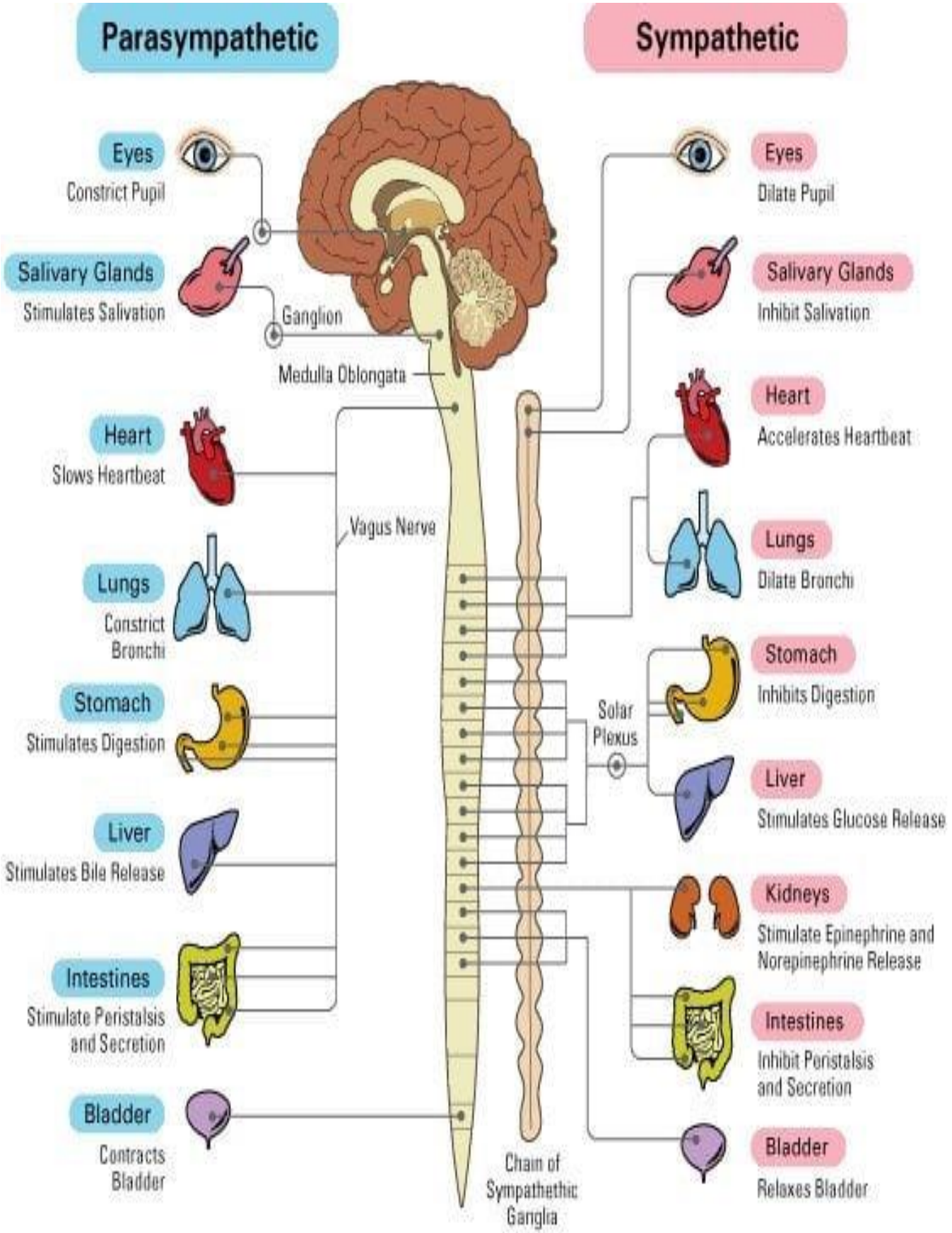
pupillae muscle and the ciliary muscle, leading to miosis (contraction of the pupil) and accommodation to near vision. The lacrimal gland receives parasympathetic innervation (sympathetic fibers are directed to the vessels), which stimulates tear secretion. The salivary gland (parotid, submaxillar and sublingual) have an important parasympathetic innervation. Stimulation of the chorda tympani evokes secretion of saliva.

The upper extremities seem to lack a parasympathetic supply. However, parasympathetic fibers are abundant in the thoracic and abdominal viscera; for the most part they are provided by the vagus nerve, increased vagal activity slows the heart. If parasympathetic stimulation is prolonged and intense, the heart may stop transiently in diastole, and during this period it is filled with blood from the large veins. Vagal fivers to the respiratory tract produce bronchial constriction and bronchial secretion when stimulated.

In the gastrointestinal tract, the general effects of the vagus are increased peristalsis and secretion as well as relaxation of sphincters. The stimulation effects on gastric secretion are well known, and severance of the vagus has been tried as therapy for peptic ulcers. Stimulation of the vagus evokes increased intestinal motility and elicits secretion by the intestinal exocrine glands. The sacral division of the parasympathetic innervates the urinary bladder, which contracts during stimulation of theses nerves. At the same time, vagal activity inhibits the action of the intestinal sphincter of the bladder. The musculature of this organ has relatively unimportant sympathetic control, although the sympathetic system does regulate its blood flow. The sacral division of the parasympathetic system also contains vasodilator fibers that go to the genitals.

In general, the actions of the sympathetic and parasympathetic system are antagonistic; if one system activates a function, the other inhibits it.

In fact, most of the vessels involved in the control of the blood pressure are innervated only by sympathetic nerves; these nerves are continuously active. The parasympathetic nerves serving blood vessels usually are restricted to small areas of the body, and vasodilator in these areas does not contribute significantly to systemic blood pressure. Therefore, to decrease blood pressure it is more important to paralyzed the continuous sympathetic activity (tone) then to elicit parasympathetic action.



Schema Explaining How Parasympathetic and Sympathetic Nervous Systems Regulate Functioning Organs

Receptor

Information about the external world and the internal environment exists in different energy forms-pressure, temperature, light, sound waves, etc. it is the function of receptors to translate these energy forms into action potentials. The rest of the nervous system can extract meaning only from action potentials or, over very short distances, from graded potentials. Regardless of its original energy form, information from receptors must be translated into the language of action potentials. The process by which stimulus energy is transformed into electrical responses in a receptors is known as transduction.

Receptors are either specialized peripheral endings of afferent neurons or separate cells that affect the peripheral ends of afferent neurons. In the former case, the afferent neuron is activated directly when the stimulus energy impinges on the specialized plasma membrane of the receptor; in the late case, the separate receptor cell contains the specialized membrane that is activated by the stimulus, and upon stimulation, the receptor cell releases a chemical messenger. This substance diffuses across the extracellular cleft separating the receptor cell from the afferent neuron. The relation between a separate receptors cell and the afferent nerve ending is similar in mechanism to the transfer of signals across a synapse.

There are many types of receptors, each of which is specific; i.e., each responds much more readily to one from of energy than to others, although virtually all receptors can be activated by several different forms of energy if the intensity is sufficient. For example, the receptors of the eye normally respond to light, but they can activated by an intense mechanical stimulus, like a poke in the eye. Note, however, that one still experiences the sensation of light in response to the poke in the eye; regardless of how the receptors is stimulated, it always gives rise to the same sensation. Thus, the sensation experienced depends on the type of receptor stimulated and not on the nature of the stimulus. This concept, that for every kind of sensation there is a special type of receptor whose activation always gives rise to that sensation, is stated as doctrine of specific nerve energies, receptors can be grouped as follows according to their location in the body:

Types of Receptor accordance to its location

1-Somatic receptors	
(a) Cutaneous receptors	On the body surface and accessible mucous membranes.
(b) Proprioceptors	In muscles, tendons and joints.
2-Visceral receptors	In the walls of blood vessels, gastrointestinal tract, bladder and other hollow viscera.
3-CNS receptors	In the brain and spinal cord.
4-Receptors of special senses	
(a) Visual receptors	In the eye
(b) Auditory receptors	In the ear
(c) Orientation receptors	In the vestibular apparatus
(d) Olfactory receptors	In the nose
(e) Gustatory receptors	In the tongue and oral mucosa

Receptors can be also be classified according to the physical nature of the stimulus, i.e. as mechanoreceptors, thermo receptors, chemoreceptors. Photoreceptors or nociceptors **(Table 3)**.

Receptor type	Adequate stimulus	Location	Examples of effective stimulus
Mechano-receptors	Mechanical deformation	Skin Muscles and tendons Joints Viscera (e.g. blood vessles, lung, stomach, bladder) Cochlea Vestibule (e.g. semi-circular cannals, utricle)	Touch, pressure, vibration Changes in muscle length and tension Joints position and movement Distension Sound vibration, about 15 Hz to 20 Hz Linear acceleration, angular acceleration
Phermo-receptors	Heart changes	Skin Hypothalamus	Warming or cooling Warming or cooling
Chemo-receptors	Certain chemicals	Carotid and arotic bodies Medulla oblongate Tongue and gut Nose Hypothalamus	Changes in plasma Po_2, PCo. pH Local changes in pH Acid, salts, sugars Odorous chemicals Changes in plasma osmolality
Thoto-receptors	Electromagnetic radiation of particular wavelength (400-700 nm)	Eye	Light
Noci-ceptors	Mechanical, thermal or chemical but only At an intensity which threatens or causes tissue damage	Skin Deep structures (muscles, joint and viscera)	Pinch, crush, sting, heat above 45-50 ^oC Excessive stretch

(B)

CHEMICAL CONTROL SYSTEM

(ENDOCRINE GLANDS)

Introduction

To function effectively, every cell in the body must communicate with its neighbors and with cells and tissues in distant portions of the body. Table (1) provides an overview of the ways our cells and tissues communicate with one another. In a few specialized tissues cellular activities are coordinated by the exchange of ions and molecules from one cell to the next across gap junctions. This direct communication occurs between cells of the same type, and the two cells must be in extensive physical contact. The two cells are communicating so closely that they function as a single entity. For example, gap junctions:

(1) Coordination ciliary movement among epithelial cells.

(2) Coordination the contraction Cardiac muscle cells.

(3) Facilitate the propagation of action potential from one neuron to the next at an electrical synapse.

Direct communication is highly specialized and relatively rare. Most of the communication between living cells involves the release and receipt of the chemical messages. Each living cell is continuously "talking" to its neighbors by releasing chemicals often called cytokines, into the extracellular fluid. These chemical tell cell what their neighbors are doing at any given moment. The result is the coordination of tissue function at the local level. Examples of these:

- **Local hormones** include the prostaglandins: this is a fatty acid secreted by one cell that alters the metabolic activates or sensitive of adjacent cells.
- **Growth hormones** this is a group of compound mainly hormones, generally peptides and these compounds responsible for stimulating and activating that promote cell division.

The use of chemical messages to transfer information from cell to cell within a single tissue is called **paracrine communication** and chemical involved are called **paracrine factor**.

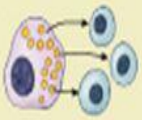
Paracrine factor enter the circulation but the concentrations are usually so low that distant cells and tissues are not affected. However, some paracrine factors, including several to the prostaglandins and related chemicals have primary effects in their tissues of origin and secondary

effectors in other tissues and organs. When secondary effects occur, the paracrine factor are also acting as hormones.

Hormones are chemical messenger that are released in one tissue and transported within the circulation to reach certain cells in other tissues. Whereas all cells release paracrine factors typical hormones are produced only specialized cells. In intercellular communication, hormones are latters, and the circulatory system is the postal service. A hormone released into the circulation will be distributed throughout the body. Each hormone has ***target cells*** that will respond to its presence. These cells process the receptors needed to blnd and "read" the hormonal message. The general pattern is indicated in **Table 1**

Table 1: mechanism of intercellular communication

TABLE 18–1 Mechanisms of Intercellular Communication

Mechanism	Transmission	Chemical Mediators	Distribution of Effects
Direct communication 	Through gap junctions	Ions, small solutes, lipid-soluble materials	Usually limited to adjacent cells of the same type that are interconnected by connexons
Paracrine communication 	Through extracellular fluid	Paracrine factors	Primarily limited to local area, where concentrations are relatively high. Target cells must have appropriate receptors
Endocrine communication 	Through the circulatory system	Hormones	Target cells are primarily in other tissues and organs and must have appropriate receptors
Synaptic communication 	Across synaptic clefts	Neurotransmitters	Limited to very specific area. Target cells must have appropriate receptors

Although every cell in the body is exposed to the mixtures of hormones in circulation at any given moment, each individual cell will respond to only a few of the hormones present. The other hormones are treated like junk mall and ignored, because the cell lacks the receptors to read the messages they contain. The use of hormones to coordinate cellular activities in tissues in distant portions of the body is called **endocrine communication**.

Because the target cells can be anywhere in the body, a single hormone can alter the metabolic activities of multiple tissues and organs simultaneously. These effects may e slow to appear, but they typically persist for days. Consequently, hormones are effective in coordination cell, tissue, and organ activities on a sustained, long-term basis. For example, circulating hormones keep body water content and levels of electrolytes and organic nutrients within normal limits 24 hours a day throughout our entire lives.

While the effects of a single hormone persist, a cell may receive additional instructions from other hormones. The result will be a further modification of cellular operations. Gradual changes in the quantities and identities of circulating hormones can produce complex changes in physical structure and physiological capabilities. Examples include the processes of embryological and fetal development, growth, and puberty.

The nervous system also relies primarily on chemical communication, but it does not use the circulation for message delivery. Instead, as we know, neurons release a neurotransmitter very close to target cells that bear the appropriate receptors. The command to release the neurotransmitter rapidly travels from one location to another in the form of **action potentials** propagated along axons. The nervous system thus acts like a telephone company, carrying high-speed "message" from one location in the body to another and delivering them to a specific destination. The effects of neural stimulation are generally **short-Lived**, and they to tend be restricted to specific target cells-primarily because the neurotransmitter is rapidly broken down or recycled. This form of **synaptic** communication is ideal for crisis management : if you are in danger of being hit by a speeding bus, the nervous system can coordinate and direct your leap to safety. Once the trisis is over and the neural circuit quiets down, things soon return to normal.

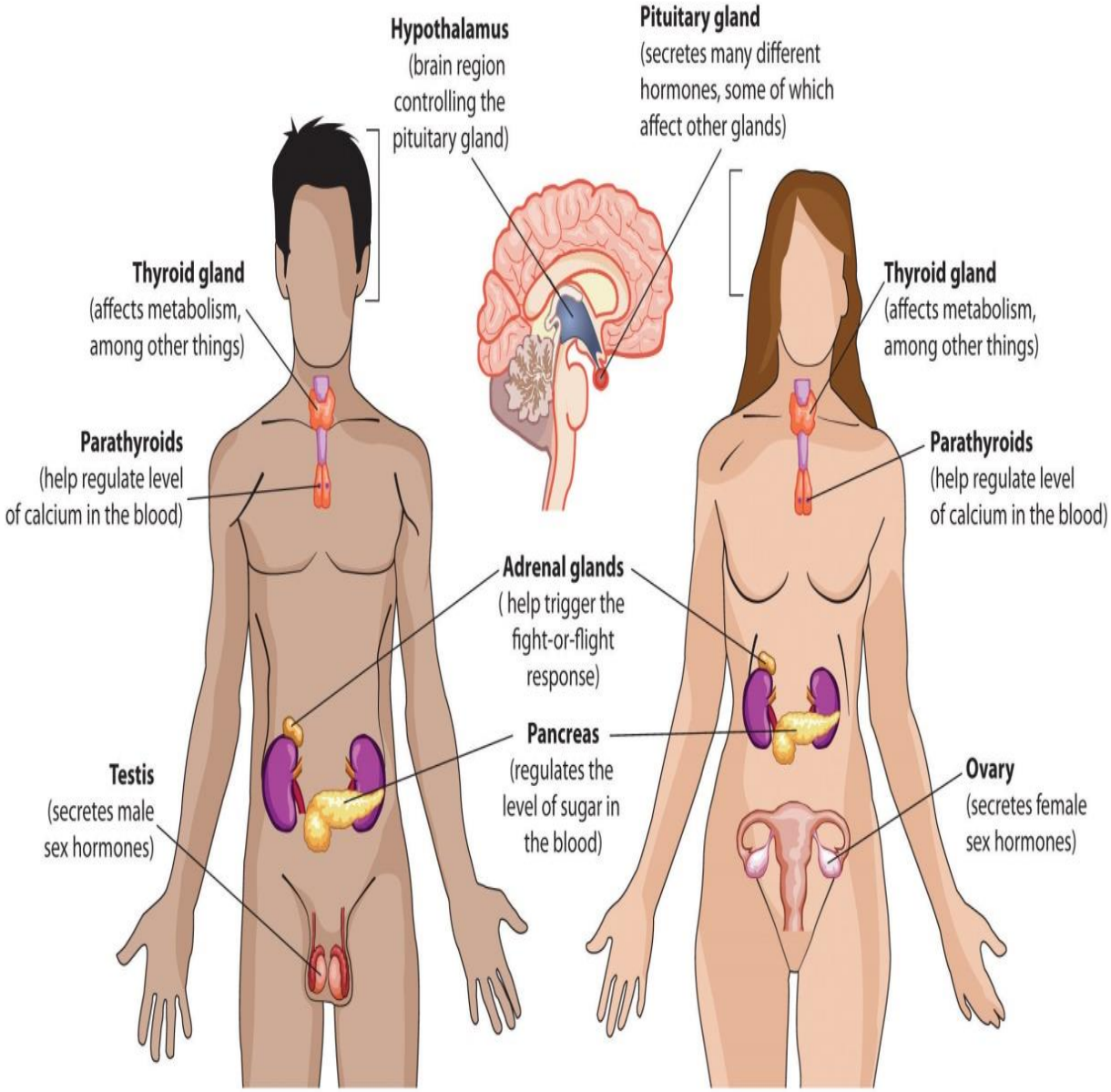
When viewed from a general perspective, the differences between the nervous and endocrine systems seem relatively clear. In fact, these broad organizational and functional distinctions are the basis for treating them as two separate systems. Yet, when we consider them in detail, the two systems are organized along parallel lines. For example:

- Both systems rely on the release of the chemicals that bind to specific receptors on their target cells.
- The two systems share many chemical massagers; for example, norepinephrine and epinephrine are called hormones when released into the circulating but neurotransmitters when released across synapses.
- Both system are regulated primarily by negative feedback control mechanisms.
- The two systems share a common goal: to preserve homeostasis by coordinating and regulating the activities of other cells, tissues, organs and systems.

We introduce the components and functions of the endocrine system and explore the interactions between the nervous and endocrine systems, and then we shall consider specific endocrine organs, hormones and functions in detail.

AN OVERVIEW OF THE ENDOCRINE SYSTEM

THE endocrine system includes all the endocrine cells and tissues of the body. As we know, **endocrine cells** are glandular secretory cells that release their secretions into the extracellular fluid. This characteristic distinguishes them from **exocrine cell**. Which secrete their products onto epithelial surfaces, generally by way of ducts. The chemicals released by endocrine cells may affect only adjacent cells, as in the case of most paracrine factors, or they may affect cells throughout the body.



• Types of hormones

(I) According to the relation between the secreting cell & the cell acted upon:-

A- Endocrine hormones

Secreted from a gland or a cell into the bloodstream that transports it to its target organ or cell.

B- Paracrine hormones

Secreted from a cell into the extracellular space & affects the neighboring cell

C- Autocrine hormone

Secreted from a cell into the extracellular space & affects the same cell that secreted it.

D- Neuroendocrine

Secreted from a nerve cell into the blood stream which transports it to its target organ or cell to relay metabolic information.

Thus it is different from a neurotransmitter that secreted by a nerve cell in a synapse to relay a nerve impulse to another nerve cell, muscle or gland.

(II) According to the chemical structure of the hormone:-

(1) Protein or peptide hormone:-

The majority of the hormones are protein hormones made up of amino acids:

a) May be short composed of only 3 amino acids or long composed of up 180 amino acids or more.
b) Composed of a linear chain or ring structure &some are composed of 2 chains.
c) Soluble in water (***hydrophilic***) & insoluble in lipid (lipophobic) e.g. insulin & glucagon.
d) They have short half-lives due to their free state in blood making them available (susceptible) to the action of ***peptidases enzymes***.

(2) Steroid hormones:-

(a) Synthesized from cholesterol & these cholesterol synthesized from the endocrine gland itself or getting it from ingested food (major source).
(b) In contrast of protein hormone, insoluble in water (hydrophobic) & soluble in lipids (**lipophilic**), for this reason they simply diffuse across the plasma membrane to the bloodstream & transported bound to plasma proteins that are specific for each hormone.
(c) The half-life is apparently enhanced by their ability to be bound to the plasma proteins.

E- Thyrosin-derived hormone:-

1- Synthesized from amino acid, tyrosine.
2- Although they are made up of an amino acid, but their properties are not similar to that of the protein hormones e.g adrenaline & noradrenalin.

F- Eicosanoids:-

1- Synthesized from fatty acids derived from arachidonic acid within the plasma membranes of most cells of the body.
2- Members of this group are:

- Prostaglandin
- Prostacyclines
- Thromboxanes
- Leukotrienes

3- They act locally either on the cell that produce them (autocrine) or pn the neighboring cell (Paracrine)
4- Their major physiological role is to:

- Control of vascular smooth muscle activity (adjust local blood flow).

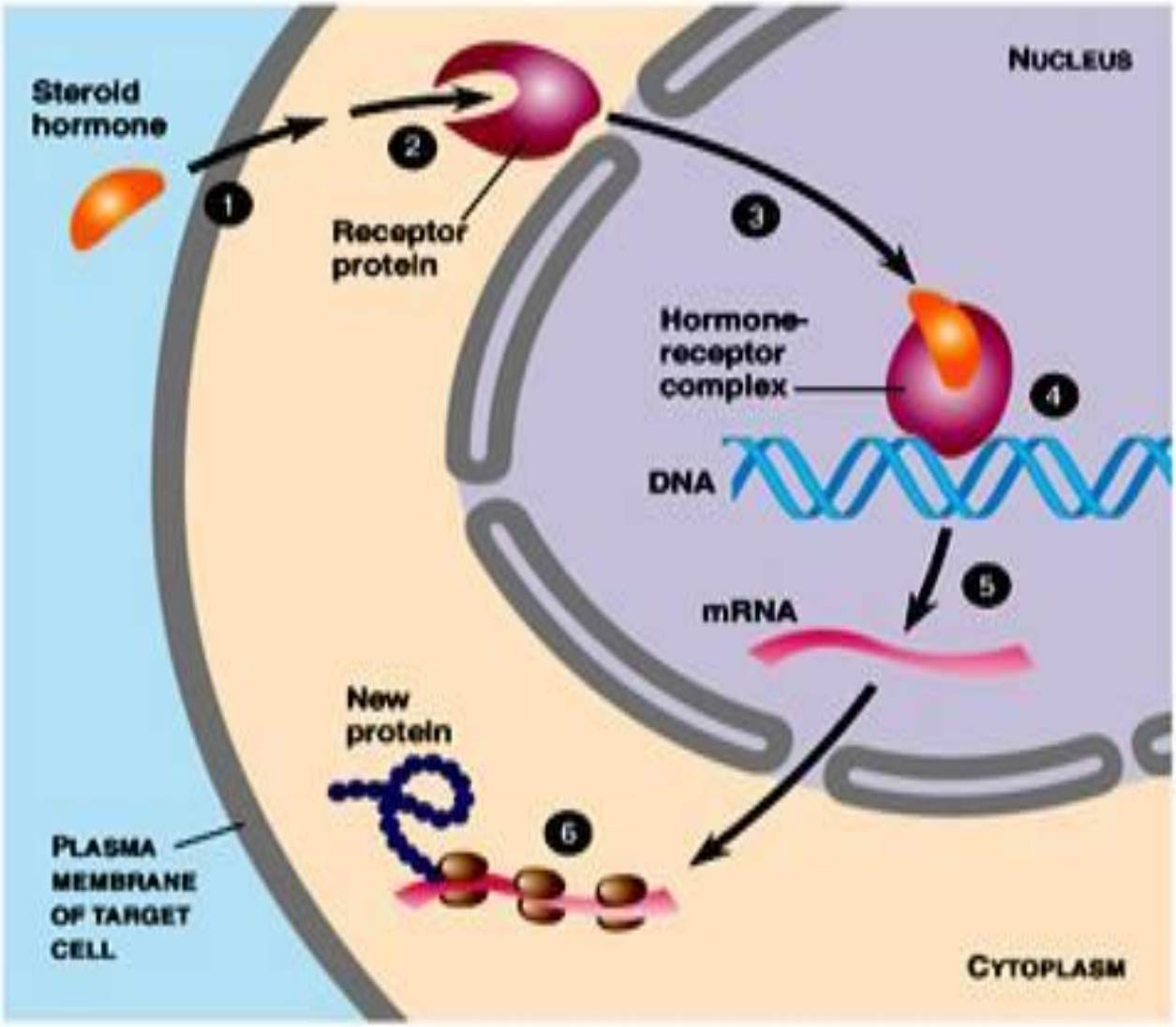
- Platelet aggregation.
- İnduce inflammatory or allergic responses.

***Mechanism of action**

1- Mechanism of the steroid hormone

- The steroid hormones including our sex hormones are lipids made from cholesterol.
- As lipids:
  - **They can diffuse through the phospholipids plasma membrane of their target cells.**
  - **Once inside a target cell a steroid hormone enters the nucleus.**
  - **Then bind to a specific receptors protein.**
  - **The hormone receptor complex then attaches to certain sites on the cell's DNA.**
  - **Activating transcription of specific genes.**
  - **Then translated into new proteins.**

- In other target cells an identical hormone-receptor complex may activate different genes; as a result different types of target cells can respond differently to the same steroid hormone.

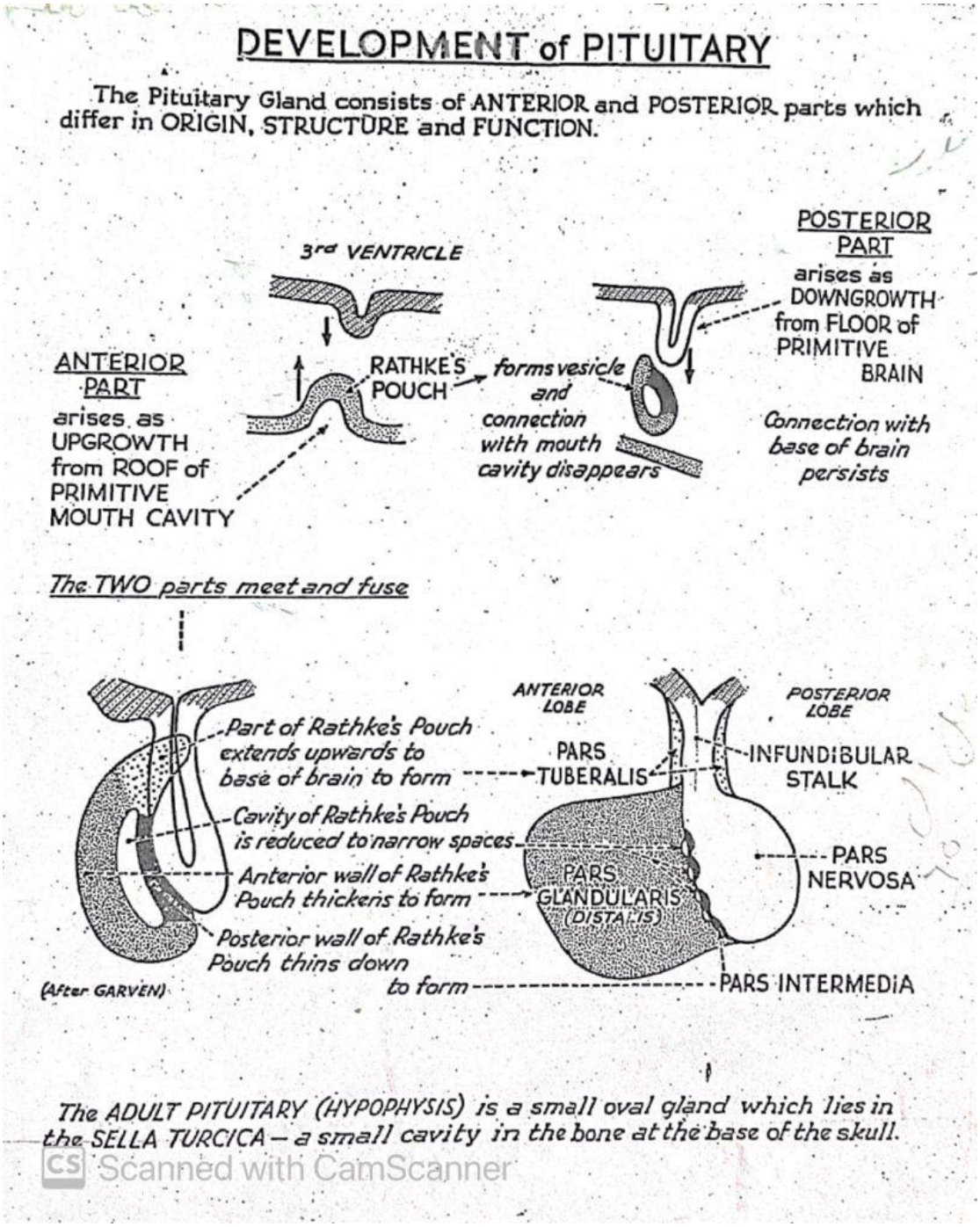


2- Mechanism of non-steroid hormone

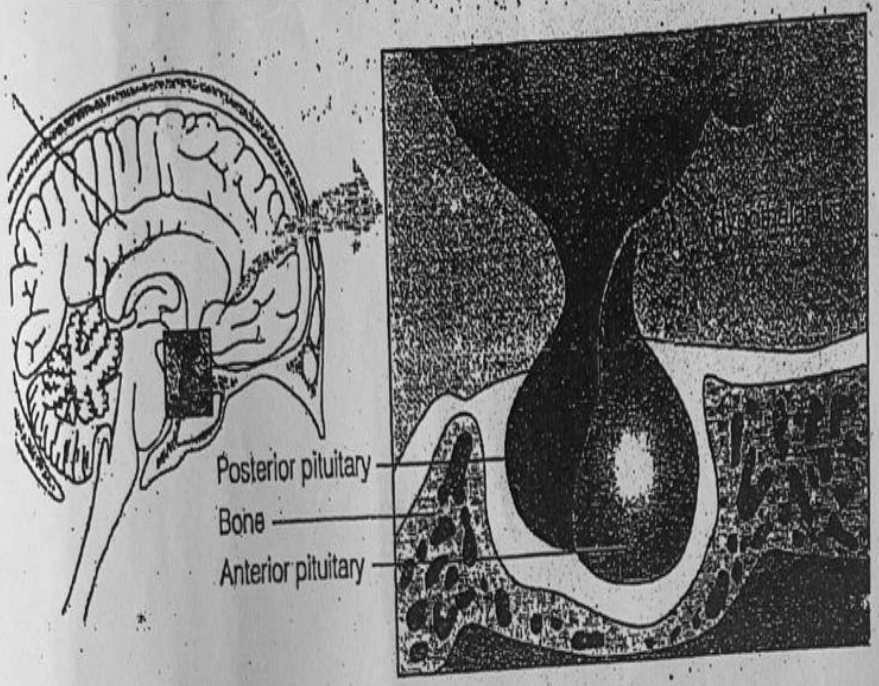
- Non steroid hormones are all synthesized from amino acids& there are three main classes of these substances.
- The amine hormones are modified versions of single amino acids.
- The peptide hormones are short chains of amino acids& are made of polypeptides having as many as 200 amino acids/
- Most nonsteroid hormones have the same basic mode of action.
- *Epinephrine* (also known as adrenaline) is an amine hormone.
- It is called the *"fight-or-flight"* hormone because it prepares the body for sudden action.
- Among other effects, it stimulates the breakdown of the energy-storage molecule glycogen in liver cells.
- *Glycogen* breakdown yields glucose which provides body cells with a ready supply of energy.
- *The epinephrine* binds to a specific receptor in the plasma membrane of a liver cell& that the binding is correlated with an increase of a compound called cAMP within the cell.
- It becomes clear that epinephrine signals the liver cell to synthesize cAMP &that cAMP then makes the cell break down glycogen.
- A hormone that has this effect on a target cell is called a first messenger.
- As:
  (1) The hormone binds to a membrane receptor protein.
  (2) Setting off a series of reaction that activate an enzyme.
  (3) The enzyme in turn converts *ATP* to *cAMP*.
  (4) cAMP serves as a second messenger; in this case triggering the breakdown of glycogen.
- The cAMP molecule is one of several types of molecule known to function as second messengers for hormones.
- In other types of cells, cAMP triggers different reactions.
- Thus, a single nonsteroid hormone can produce different response in different target cells as can a steroid hormone.

THE PITUITARY GLAND

The pituitary gland can divided into posterior and anterior divisions on the basis of function and development anatomy. Nine important peptide hormones are released by the pituitary gland seven by the anterior pituitary and two by posterior pituitary. Ala nine hormones bind to membrane receptors and all nine use cAMP as a second messenger.



Pituitary gland hypothalamus axis



Location of hypothalamus & pituitary

Blood supply

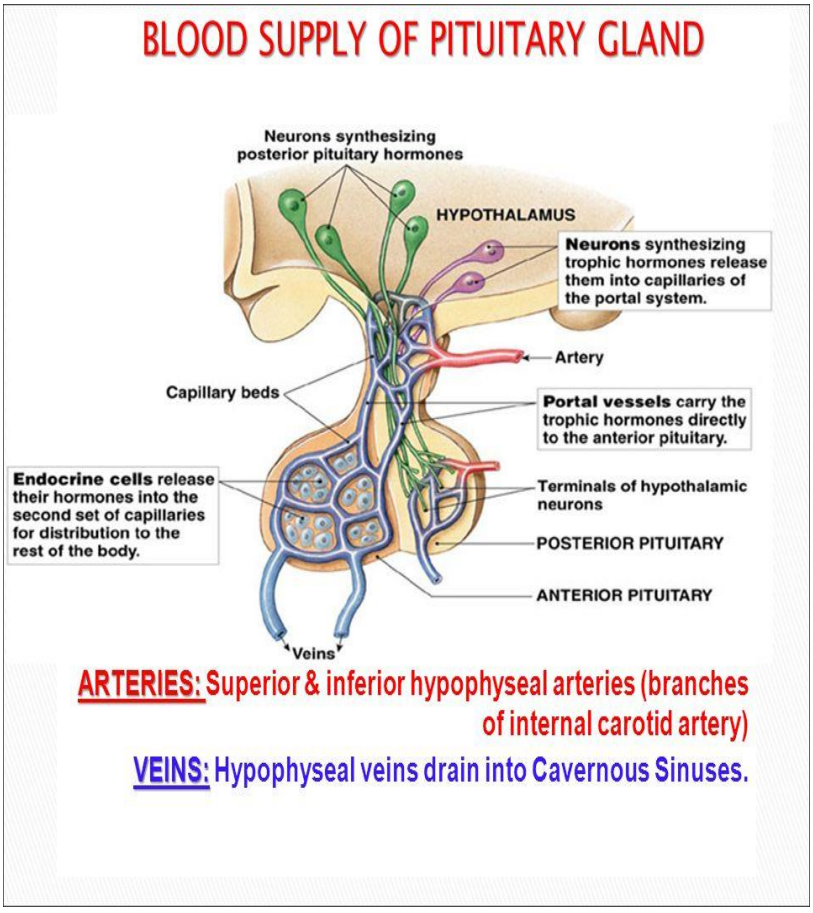
Arterial blood

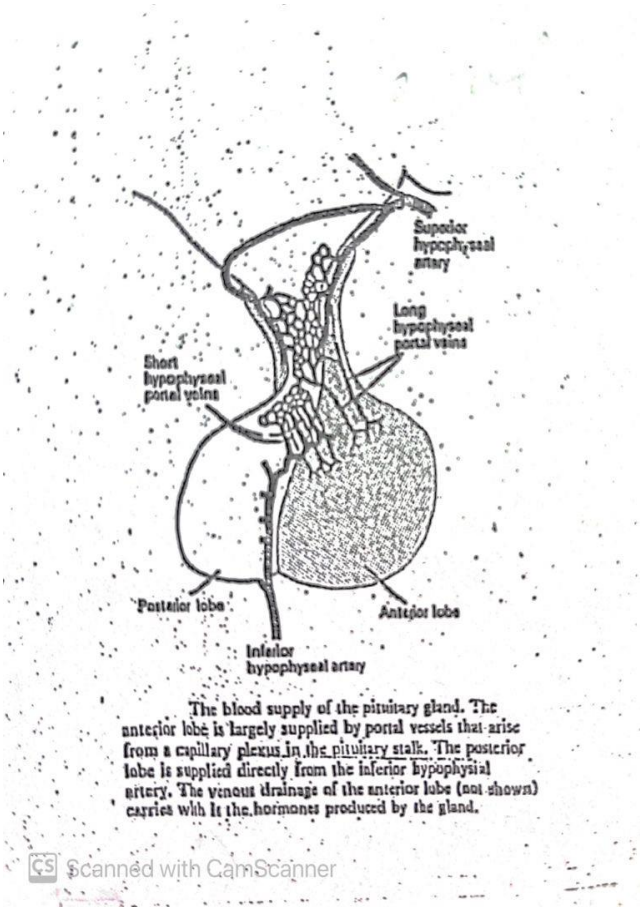
This is supplied by branches from the internal carotid artery.

The anterior lobe is supplied ***indirectly*** by blood that has already passed through a capillary bed in the hypothalamus but the posterior lobe is supplied ***directly***.

Venous blood

This comes from both lobes, containing hormones& leaves the gland in short veins that enter the venous sinuses between the layers of dura mater.





❖ *The Anterior pituitary*

The anterior pituitary, or **adenohypophysis**, contains a variety of endocrine cell types. The anterior pituitary can be subdivided into three regions:

(1) A pars distal (distal part), which is the largest portion of the entire pituitary gland.
(2) An extension called the **pars tuberalis**, which wraps around the adjacent portion of the infundibulum.
(3) A slender **pars intermedia** (intermediate part), which forms a narrow band bordering the posterior pituitary.

An extensive capillary network radiates through these regions, so every endocrine cell has immediate access to the circulatory system.

Hypothalamic Control of the Anterior Pituitary (hypothalamic-pituitary axis)

There are two classes of regulatory hormones:

(1) Releasing hormones (RH): stimulates synthesis and secretion of one or more hormones at the anterior pituitary.
(2) Inhibiting hormones (LH): prevents the synthesis and secretion of hormones from the anterior pituitary.

An endocrine cell in the anterior pituitary may be controlled by releasing hormones, inhibiting hormones, or some combination of the two. The regulatory hormones released at the hypothalamus are transported directly to the anterior pituitary by the hypophyseal portal system.

The rate of regulatory hormone secretion by the hypothalamus is controlled by **a negative feedback**.

Table (3) Hormones of the hypothalamus, anterior pituitary & their target tissues

Hypothalamus	anterior pituitary	target gland or tissue
GHRH	GH	Most tissues
		Many tissues
GHRIH	GH inhibition	thyroid gland
	TSH inhibition	pancreatic islets
		Most tissues
TRH	TSH	thyroid gland
CRH	ACTH	Adrenal cortex
PRH	PRL	Breast
PIH	PRL inhibition	Breast
LHRH	FSH	ovaries & testes
GnRH	LH	ovaries & testes

GHRH= growth hormone releasing hormone
GH= growth hormone (somatotrophin)
GHRIH= growth hormone release inhibiting hormone (somatotrophin)
TRH= thyroid releasing hormone
TSH= thyroid stimulating hormone
CRH= corticotrophin releasing hormone
ACTH= adrenocorticotrophic hormone
PRH= prolactin releasing hormone
PRL= prolactin (lactogenic hormone)
PIH= prolactin inhibiting hormone (dopamine)
LHRH= luteinizing hormone releasing hormone
GnRH= gonadotrophin releasing hormone
FSH= follicle stimulating hormone
LH= luteinizing hormone

Hormones of the Anterior Pituitary

We will discuss seven hormones whose functions and control mechanisms are reasonably well understood: thyroid stimulating hormone, adrenocorticotropic hormone, follicle-stimulating hormone, luteinizing hormone, prolactin, growth hormone, and melanocyte-stimulating hormone. Of the six hormones produced by the pars distalls, four regulated the production of hormones by other endocrine glands. The names of these hormones indicate their activities, by many the phrases are so long that abbreviations are often used instead.

The hormones of the anterior pituitary are so called tropic hormones, because they turn on endocrine glands or support the functions of other organs. (some references use trophic hormones to refer to these hormones).

(1) Thyroid –stimulating hormone (TSH)

Thyroid-stimulating hormone (TSH), or thyrotropin, targets the thyroid gland and triggers the release of thyroid hormones. TSH is released in response to thyrotropin-releasing hormones (TRH) from the hypothalamus. As circulating concentrations of thyroid hormones rise, the rates of TRH and TSH production decline.

(2) Adrenocorticotropic hormone (ACTH)

Adrenocorticotropic hormone (ACT), also known as corticotrophin, stimulates the release of steroid hormones by the adrenal cortex, the outer portion of the adrenal gland. ACTH specially targets cells that hormones called glucocorticoids, which affect glucose metabolism. ACTH release occurs under the stimulation or corticotrophin.

Releasing hormone (CRH) from the hypothalamus. As glucocorticoid levels increase, the rates of CRH and ACTH release decline.

(3) The Gonadotropins

Follicle-stimulating hormone and luteinizing hormone are called gonadotropins, because they regulate the activities of the male and female gonads (testes and ovaries, respectively). the production of gonadotropins occur under stimulation by gonadotropin-releasing hormone (GnRH) from the hypothalamus.

1- ***Follicle-stimulating hormone (FSH) or follitropin***, promotes follicle development in women and, in combination with luteinizing hormone, stimulates the secretion of estrogen by ovarian cell. ***Estradiol*** is the most important estrogen. In men, FSH stimulates ***sustentacular cells***, specialized cells in the tubules where sperm differentiate. In response, the sustentacular cells promote the physical maturation of developing sperm. FSH production is inhibited by inhibin, a peptide hormone released by cells in the testes and ovaries figure (10a). (Disagreement existes as to whether inhibin suppresses the release of GnRH as well as FSH).

2- ***Luteinizing Hormone (LH) or Lutropin***, induces ovulation in women and promotes the ovarian secretion of estrogen and the ***progestins*** (such as progesterone), which prepare the body for possible pregnancy. N men, LH is sometimes called ***interstitial cell0stimulating hormone (ICSH)***, because it stimulates the production of sex hormones by the *interstitial cells* of the testes. These sex hormones are called **androgens** (andors, amn), the most important of which is testosterone, LH production, like FSH production, is stimulated by **GnRH** from the hypothalamus. GnRH production is inhibited by estrogen, progestin, and androgen Figure

(4) Prolactin (PRL)

Prolactin or mammotropin, works with other hormones to stimulate mammary gland development. In pregnancy and during the nursing period that follows delivery, PRL also stimulates milk production by the mammary glands. The functions of PRL in the regulation of androgen production. (PRL appears to make interstitial cells more sensitive to LH).

Prolactin production is inhibited by **prolactin-inhibiting hormone (PIH).** This hormone is identical to the neurotransmitter ***dopamine***. The hypothalamus also secrets a **prolactin-releasing hormones**, but the identity of this ***prolactin-releasing factor (PRF)*** is a mystery. Circulating PRL stimulate PIH release and inhibits the secretion of prolactin-releasing factor.

Although PRL exerts the dominant effect on the glandular cells, normal development of the mammary glands is regulated by the interaction of several hormones. Prolactin, estrogen, progesterone, glucocorticoids, pancreatic hormones, and hormones produced by the placenta cooperate in preparing the mammary glands for secretion, and milk ejection occurs only in response to oxytocin release at the posterior pituitary.

(5) Growth Hormone

Growth hormone (GH), or somatotropin (*soma*, body), stimulate cell growth and replication by accelerating the rate of protein synthesis. Although virtually every tissue responds to some degree, skeletal muscle cells and chondrocytes (cartilage cells) are particularly sensitive to GH levels.

The stimulation of growth by GH involves two different mechanisms:

1- The pituitary mechanism, which indirect, is best understood. Liver cells respond to the presence of GH by synthesizing and releasing insulin-like growth factor (IGFs), or **somatomedins**, which are peptide hormones that ind to receptor sites on a variety of cell membranes. in skeletal muscle fibers, cartilage cells, and other target cells, somatomedins increase the rate of uptake of amino acids and their incorporation into new proteins. These effects develop almost immediately after GH release occurs; they are particularly important after a meal, when the blood contains high concentrations of glucose and amino acids. In functional terms, cells can now obtain ATP easily through the aerobic metabolism of glucose, and amino acids are readily available for protein synthesis. Under these conditions, GH, acting through the somatomedins, stimulates protein synthesis and cell growth.

2- The direct action of GH are more selective and tend not to appear until after blood glucose and amino acid concentrations have returned to normal levels:

- In epithelia and connective tissues, GH stimulates stem cell division and differentiation of daughter cells will be stimulated by somatomedins.
- **GH also has metabolic effects in adipose tissue and in the liver**. In adipose tissue, GH stimulate the breakdown of stored triglycerides by adipocytes (fat cells), which then release fatty acids into the blood. As circulating fatty acid levels rise, many tissues stop breaking down glucose and start breaking down fatty acids to generate ATP. This process is termed a glucose-sparing effect. In the liver, GH stimulates the breakdown of glycogen reserves by liver cells. These cells then release glucose into the circulation. Because most other tissues are now metabolizing fatty acids rather than glucose, blood glucose concentrations begin to climb, perhaps to levels significantly higher than normal. The elevation of blood glucose levels by GH has been called a **diabetogenic effect**, because *diabetes mellitus*, an endocrine disorder we will consider later in the chapter, is characterized by abnormally high blood glucose concentrations.

Control of growth hormone production

The production of GH is regulated by:

(1) **Growth hormone-releasing hormone** (GH-RH, or somatocrinin) from hypothalamus.
(2) **Growth hormone- inhibiting hormone** (GH-IH, or somatostatin) from the hypothalamus.
(3) **Somatomedins or insulin-like growth factor** (IGFs) from the liver stimulate GH-IH and inhibit GH-RH.

Melanocyte-stimulating hormone (MSH)

The pars intermedia may secret two forms of melanocyte-stimulating hormone (MSH), or melanotropin. As the name indicates, MSH stimulates the melanocytes of the skin, increasing their production of melanin, a brown, black, or yellow-brown pigment. MSH release is inhibited by **an inhibiting hormone** now known to **dopamine**. MSH is important in the control of skin pigmentation in fishes, amphibians,

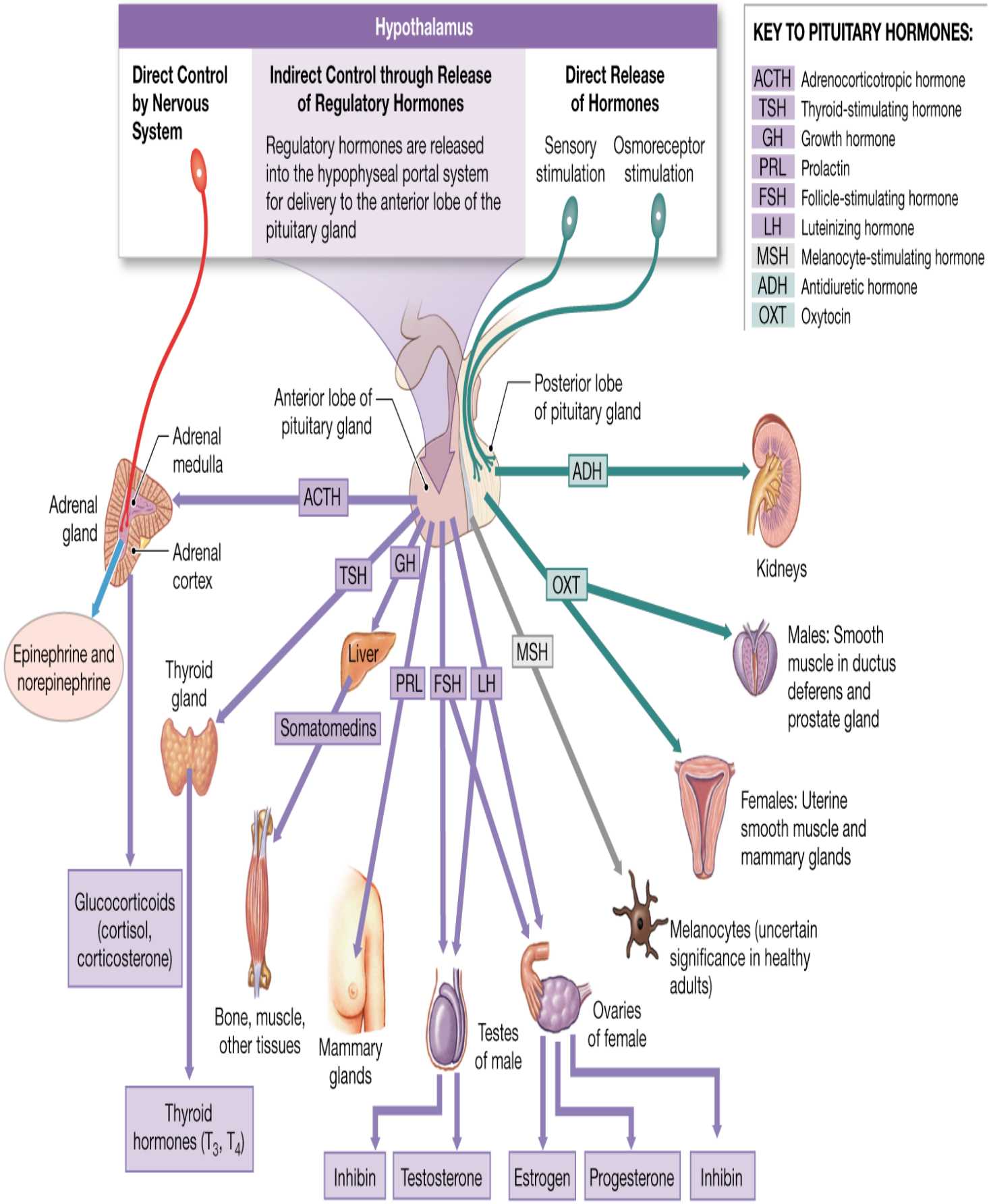
reptiles, and many mammals other than primates. The pars intermedia in adult humans is virtually nonfunctional, and the circulating blood usually does not contain MSH. Moreover, MSH is secreted by the human pars intermedia:

1- During fetal development
2- In very young children
3- In pregnant women
4- In some disease states.

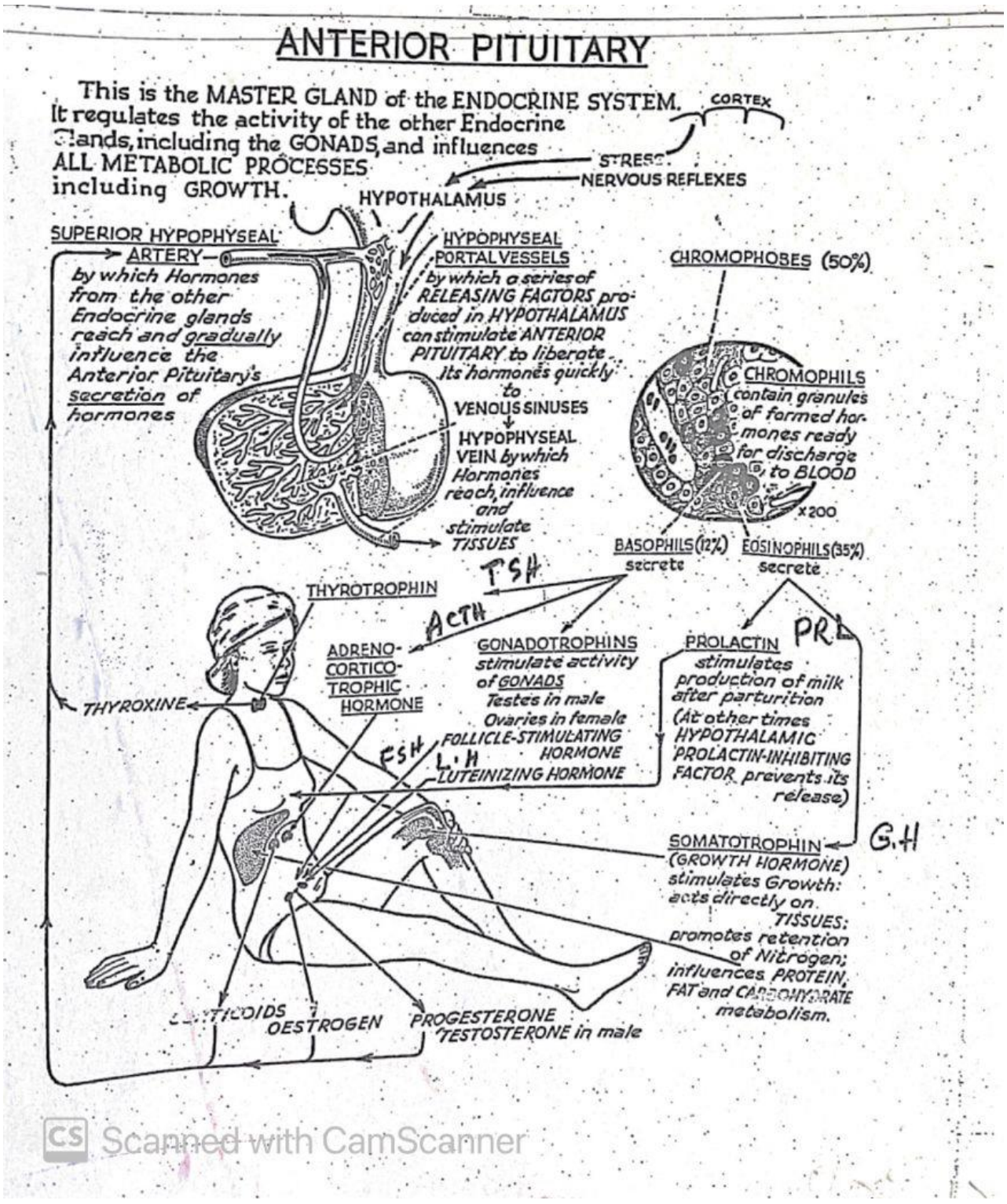
The functional significance of MSH secretion under these circumstances is not known. Administration of a synthetic form of MSH causes darkening of the skin, and it has been suggested as a means of obtaining a "sunless tan".

(6) Endorphins

Endorphins (endogenous morphine) are endogenous opioid peptide that function as neurotransmitters. They are produced by the pituitary gland and hypothalamus in vertebrates during exercise, excitement, pain, consumption of spicy food, and orgasm and they resemble the opiates in their abilities to produce analgesia and a feeling of well-being. This hormone acts on the receptors of pain in the brain to decline the pain.


Hypothalamus
Direct Control by Nervous System
Indirect Control through Release of Regulatory Hormones
Regulatory hormones are released into the hypophyseal portal system for delivery to the anterior lobe of the pituitary gland
Direct Release of Hormones
Sensory stimulation
Osmoreceptor stimulation
KEY TO PITUITARY HORMONES:
ACTH Adrenocorticotropic hormone
TSH Thyroid-stimulating hormone
GH Growth hormone
PRL Prolactin
FSH Follicle-stimulating hormone
LH Luteinizing hormone
MSH Melanocyte-stimulating hormone
ADH Antidiuretic hormone
OXT Oxytocin
Anterior lobe of pituitary gland
Posterior lobe of pituitary gland
Adrenal medulla
Adrenal gland
Adrenal cortex
ACTH
ADH
Kidneys
TSH
GH
OXT
Males: Smooth muscle in ductus deferens and prostate gland
Epinephrine and norepinephrine
Thyroid gland
Liver
MSH
PRL
FSH
LH
Somatomedins
Females: Uterine smooth muscle and mammary glands
Glucocorticoids (cortisol, corticosterone)
Melanocytes (uncertain significance in healthy adults)
Bone, muscle, other tissues
Mammary glands
Testes of male
Ovaries of female
Thyroid hormones (T_3, T_4)
Inhibin
Testosterone
Estrogen
Progesterone
Inhibin

ANTERIOR PITUITARY



Region/ Area	Hormones	Targets	Hormonal Effects	Hypothalamic Regulatory Hormones
Anterior pituitary (Adenohypophysis)				
Pars distalis	Thyroid-stimulating Hormone (TSH)	Thyroid Gland	Secretion of thyroid hormones	Thyrotropin-releasing hormone (TRH)
	Adrenocorticotropic Hormone (ACTH)	Adrenal cortex (zona fasciculate)	Glucocorticoid secrtion	Cortictropin-releasing hormone (CRH)
	Gonadotropic hormones:			
	Follicle- stimulating hormone (FSH)	Follicle cells of ovaries	Estrogen secretion follicle development	Gonadotropin-releasing hormone (GnRH)
		Sustentacular cells of testes	Stimulation of sperm maturation	As above
	Luteinizing hormone (LH)	Follicle cells of ovaries	Ovulation formation of corpus luteum, progesterone secretion	As above
		Interstitial cells of testes	Testosterone secretion	As above
	Prolactin (PRL)	mammary glands	Production of milk	Prolactin-inhibiting hormone (PIH)
				Prolactin-releasing factor (PRF
	Growth hormone (GH)	All cells	Growth, protein, synthesis, lipid, mobilization and catabolism	Growth hormone, releasing hormone (GH-RH
				Growth hormone-inhibiting hormone (GH-IH)
Pars intermedia (not active in normal adults)	Melanocyte-stimulating hormone (MSH)	Melanocytes	Increased melanin synthesis in epidermis	Melanocyte-stimulating hormone- inhibiting hormone (MSH-IH)

The Posterior Pituitary

The posterior pituitary is also called the **neurohypophysis**, or **pars nervosa** (nervous part), because it contains the axons of hypothalamic neurons. Neuron of the supraoptic and periventricular nuclei manufacture **antidiuretic hormone (ADH)** and oxytocin, respectively. These products move by axoplasmic transport along axons in the infundibulum to the basement membranes of capillaries in the posterior pituitary gland.

(1) Antidiuretic Hormone

Antidiuretic hormones (ADH), also known as vasopressin or arginine vasopressin (AVP), is released in response to a variety of stimuli, most notably a rise in the electrolyte concentration in the blood or a fall in blood volume or blood pressure. A ruse in the electrolyte concentration stimulates the secretory neurons directly. Because they respond to a change in the osmotic concentration of body fluids, these neurons are called ***osmoreceptors***. ADH secretion after a fall in blood volume or pressure occurs under the stimulation of another hormone, ***angiotensin II***.

The primary function of ADH is to decrease the amount of water lost at the kidneys. With losses minimized, any water absorbed from the digestive tract will be retained, reducing the concentration of electrolytes in the extracellular fluid. In high concentrations, ADH also causes ***vasoconstriction***, a constriction of peripheral blood vessels that helps elevate blood pressure, ADH release is inhibited by alcohol, which explains the increased fluid extraction that follows the consumption of alcoholic beverages.

(2) Oxytocin (OT)

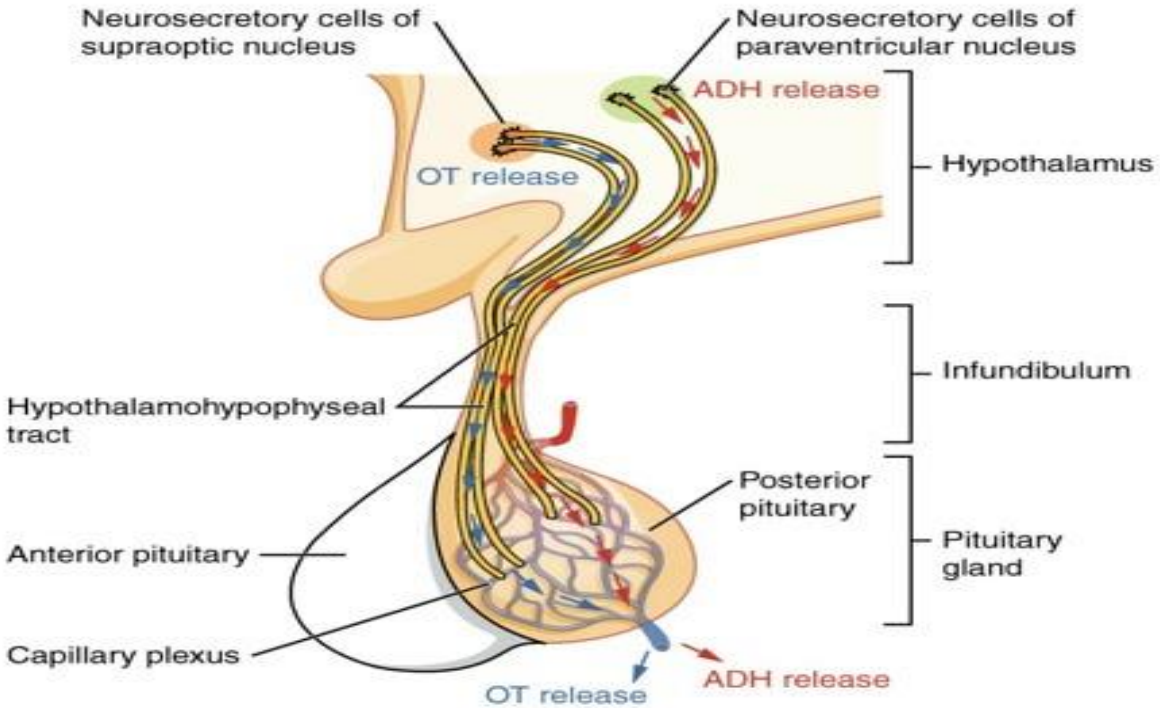
In women, oxytocin or OT, stimulates smooth muscle tissue in the wall of the uterus, promoting labor and delivery. After delivery, oxytocin stimulates the concentration of myoepithelial cells around the secretory alveoli and the ducts of the mammary glands, promoting ejection of milk.

Until the last stages of pregnancy, the uterine smooth muscles are relatively insensitive to oxytocin, but sensitivity becomes more pronounced as the time of delivery approaches. The trigger for normal labor and delivery is probably a sudden rise in oxytocin levels at the uterus. There is good evidence, however, that the oxytocin involved is secreted by the uterus and fetus.

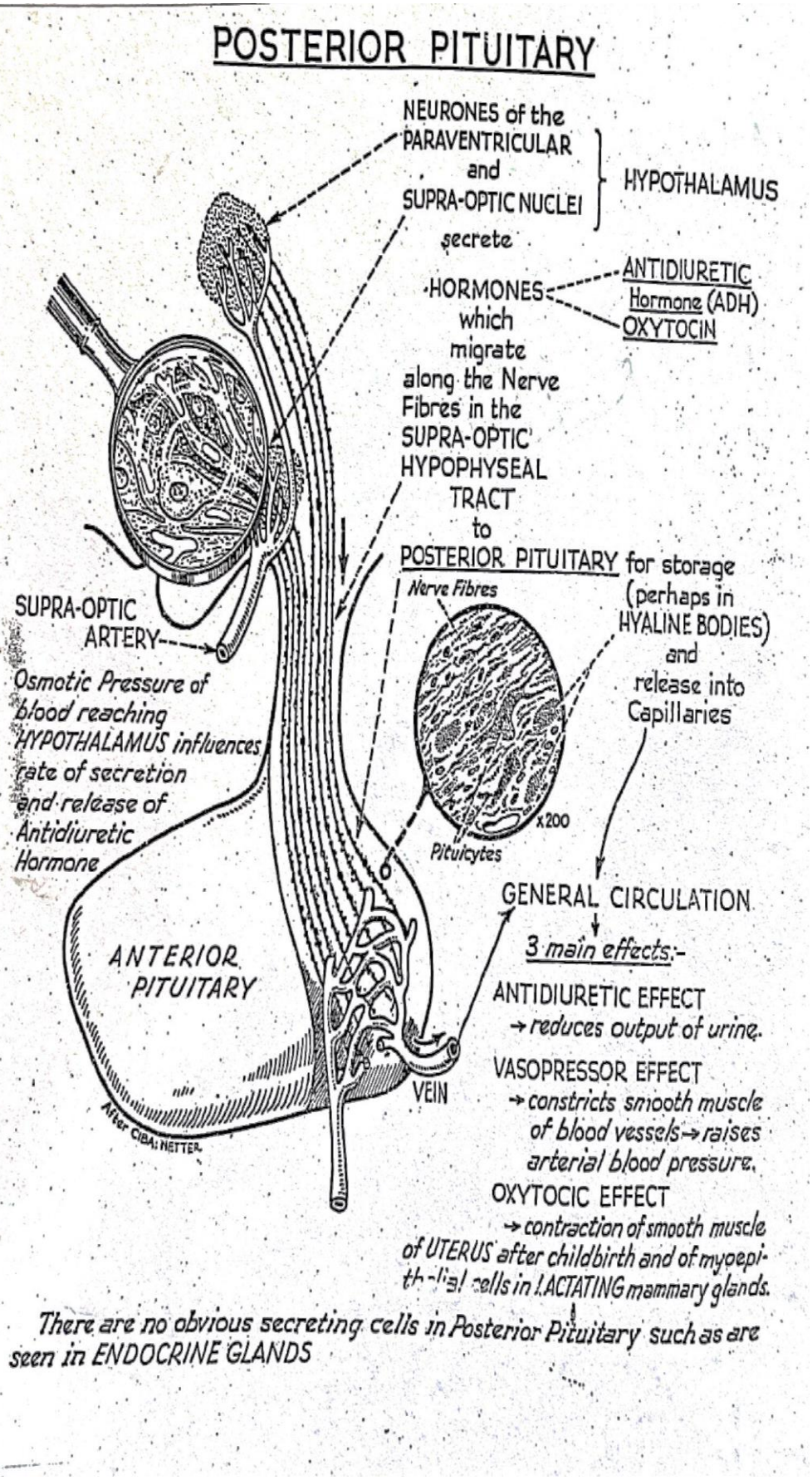
Oxytocin secretion and milk ejection are part of the neuroendocrine reflex the stimulus is an infant suckling at the breast, and sensory nerves innervating the nipples relay the information to the hypothalamus. Oxytocin is then release into the circulation at the posterior pituitary, and the myoepithelial cells respond by squeezing milk from the secretory alveoli into large collecting ducts. This "milk let-down" reflex can be modified by any factor that affects the hypothalamus. For example, anxiety, stress and other factors can prevent the flow of milk, even when the mammary gland are fully functional. In contract, nursing mothers can become conditioned to associated a body's crying with suckling these women may begin milk let-down as soon as they hear a baby cry.

Although the function of oxytocin in male and female sexual activity remain uncertain, it is known that circulating concentrations of oxytocin in both genders rise during sexual arousal and peak at orgasm. There is evidence that in men oxytocin stimulates smooth muscle concentrations in the walls of the sperm duct (*ductus deferens*) and prostate gland. These actions may be important in *emission*, the ejection of prostatic secretions, sperm, and the secretion of other glands into the male reproductive tract before ejaculation. There are indications that the oxytocin released during intercourse in females may stimulate smooth muscle concentrations in the uterus and vagina that promote sperm transported toward the uterine tubes.

Posterior pituitary (neurohypophysis or Pars Nervosa)				
	Antidiuretic hormone (ADH)	Kidneys	Reabsorption of water, elevation of blood volume and pressure	Transported along axons from supraoptic nucleus to posterior pituitary gland
	Oxytocin (OT)	Uterus, mammary glands (females)	Labor contractions, milk ejection	Transported along axons from paraventricular nucleus to posterior pituitary gland
		Ductus deferens and prostate gland (males)	Contractions of ductus deferens and prostate	



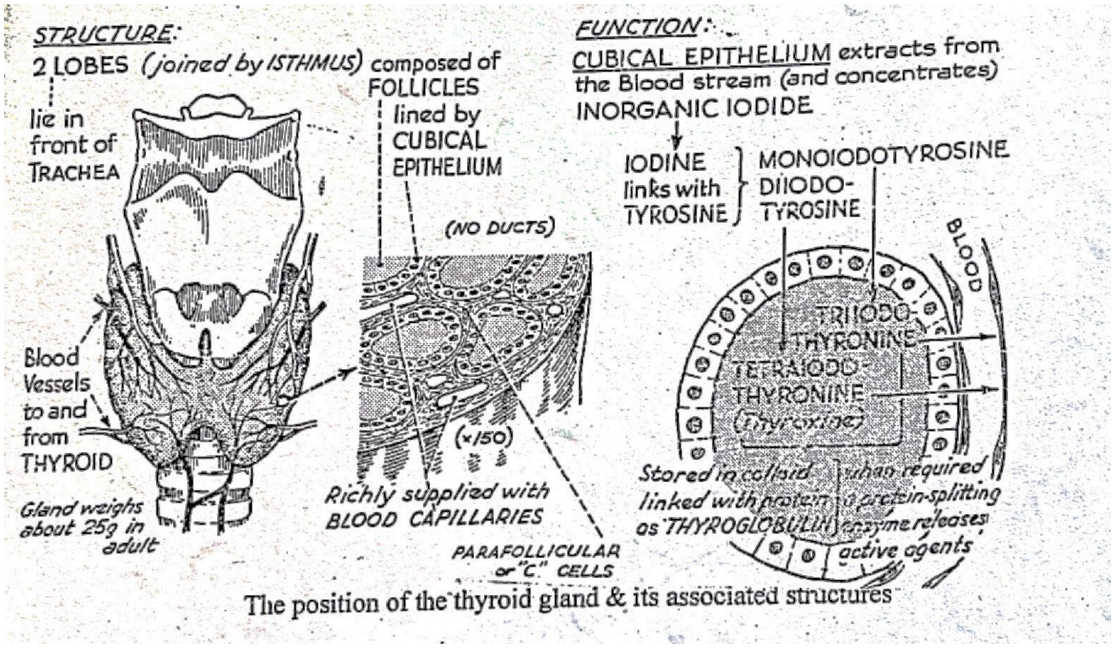
POSTERIOR PITUITARY



There are no obvious secreting cells in Posterior Pituitary such as are seen in ENDOCRINE GLANDS

Thyroid gland

- The thyroid gland is situated in the neck in front of the larynx& trachea at level of the 5th, 6th&7th cervical& 1st thoracic vertebrae.
- It is a highly vascular gland that weighs about 25 g& is surrounded by ***a fibrous capsule***.
- It resembles as a butter fly in shape, consisting of ***two symmetrical lobes***, one on either side of the thyroid cartilage & upper cartilaginous rings of the trachea.
- The lobes are joined by a narrow ***isthmus***.
- The lobes are roughly ***cone-shaped***, about 5 cm long & 3cm wide.



The position of the thyroid gland & its associated structures

- The thyroid gland is composed of cuboidal epithelial that forms ***spherical follicles***.
- These secret & store ***colloid***, a thick sticky protein material.
- Between the follicles there are other cells found singly or in small groups. ***Parafollicular cells*** also called ***C-cells*** which secrete ***the hormone calcitonin***.

The arterial blood supply

- The arterial blood supply to the gland is through the superior & inferior thyroid arteries.
- The superior thyroid artery is a branch of ***the external carotid artery***.
- The inferior thyroid artery is a branch of ***subclavian artery***.

The venous return

The venous return is by the thyroid veins which drain into ***the internal jugular veins***.

- ***Two parathyroid glands*** lie against the posterior surface of each lobe & are sometimes embedded in thyroid tissue.

Thyroid gland secrets 3 hormones:

- Two thyroid hormones thyroxin (tetraiodothyronin T_4) & (triiodothyronin T_3).
- Calcitonin.
- Adult human thyroid gland weighing 10-29gm & it is the largest gland in human body, usually ***larger*** in woman than man.

The thyroid hormones

- Composed of tyrosine molecules.
- They contain the trace element iodine.

The active hormones are:

(1) ***Thyroxine*** (tetra iodothyronine **T4**)
Composed of 2 molecules of thyrosin+ iodine atoms (**T4**).

(2) ***Triiodothyronine*** (**T3**)
Composed of 2 molecules of thyrosin+3 iodine atoms (**T3**).

- Iodine is essential for the formation of the thyroid gland hormones T3&T4.
- The body's main sources of iodine are sea food, vegetables grown in iodine rich soil & iodinated table salt in the diet.
- The thyroid gland selectively takes up iodine from the blood, a process called ***iodine trapping***.
- The thyroid hormones are synthesized as large precursor molecules called thyroglobulin, the major constituent of colloid.

Regulation of the thyroid hormones

- The synthesis & secretion of thyroid hormones are regulated by ***the anterior pituitary thyrotrophin, TSH***.
- The secretion of ***TSH*** is stimulated by the ***TRH*** from the hypothalamus & secretion of ***TRH*** is stimulated by exercise, stress, malnutrition, low plasma glucose & sleep.

The output of TSH influenced by:

(1) *TRH*.
(2) Inhibitory hormones somatostatine ***GHRIH*** from hypothalamus.
(3) Blood level of ***T3***, ***T4***.

- Increased levels of T3 &T4 exert a negative feedback mechanism at the level of both the hypothalamus &pituitary, where they inhibit TRH from the hypothalamus which diminishes TSH secretion from pituitary.
- At the same time they themselves ***inhibit TSH*** secretion from the pituitary.
- ***The decreased TSH*** will decrease the synthesis & release of thyroid hormones.
- When the supply of iodine is deficient; ***excess TSH*** is secreted & there is proliferation of thyroid gland cells & enlargement of the gland.
- Secretion of T3 &T4 begins about the third month of fetal life & is increased at puberty & in women during the reproductive years, especially during pregnancy; otherwise it mains fairly constant throughout life.

Action of thyroid hormone

(1) Thyroid hormone enters the target cells & regulates the expression of gens in the nucleus, i.e. they increase or decrease the synthesis of some protein including hormones.
(2) They combine with specific receptor sites &enhance the effects of other hormones e.g. adrenaline & noradrenaline.

(I.e. thyroid hormones are often required for the actions of other hormones).

(3) Thyroid hormones have general metabolic effects particularly important in promoting normal growth & development.

(4) Regulation a number of homeostatic functions including energy & heat production.

(5) Regulation metabolism of carbohydrates, proteins & fats.

(6) Maintain normal blood pressure, heart rate, muscle tone, digestion &reproductive functions.

(7) They are unique in that they exert effects within almost every tissue of the body throughout the life of the animal.

Regulation of the thyroid hormones

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The secretion of TSH is stimulated by the TRH from the hypothalamus & secretion of TRH is stimulated by exercise, stress, malnutrition, low plasma glucose &sleep.

Calcitonin has 3 effects:

(1) It causes more Ca2+ to be deposited in the bones & reuce the reabsorption of calcium from bones.
(2) It makes the intestine absorb less Ca2+ from the diet.
(3) It makes the kidneys reabsorb less Ca2+ as they form urine.

- The results are a lower Ca2+ level in the blood.
- CT is important during childhood when bines undergo considerable changes in size &shape.

Calcitonin is probably most important during childhood, when it stimulates bone growth and mineral deposition in the skeleton. It also appears to be important in reducing the loss of bone mass:

(1) During prolonged starvation.
(2) In the late stages of pregnancy, when the maternal skeleton competes with the developing fetus for calcium ions absorbed by the digestive tract.

Parathyroid gland and parathyroid hormone

The parathyroid glands arose relatively recently in vertebrate evolution , they are not found in fish and are seen in amphibians such as the salamander only after metamorphosis to the land-dwelling form.

The importance of the parathyroid in normal calcium economy was established during the latter part of the nineteenth century when it was found that parathyroidectomy resulted in lethal tetany.

Human begins typically have four parathyroid glands, but as few as two and as many as eight have been observed. These glands adhere to the posterior surface of the thyroid gland or occasionally are embedded within thyroid tissue.

Parathyroid glands are composed of two cell types (*Chief cells*) predominant and are arranged in clusters or cords. They are the source of PTH and have all of the cytological characteristics of cells that produce protein hormones. Rough endoplasmic reticulum, prominent Golgi apparatus, and some membrane-bound storage granules. *Oxyphil cells* which appear singly or in small groups, are larger than chief cells and contain a remarkable number of mitochondria. Oxyphil cells have no known function and are thought by some to be degenerated chief cells.

Physiological actions of parathyroid hormone:

Parathyroid hormone is the principle regulator of the extracellular calcium pool. It increases the calcium concentration and decreases the phosphate concentration in blood by various direct and indirect actins on bone, kidney and intestine. In its absence, the concentration of calcium in blood and hence interstitial fluid, decreases dramatically over a period of several hours while the concentration of phosphate increases.

Hypoparathyroidism may result from insufficient production of active hormone or defects in the responses of target tissues; acutely, all the symptoms of hypocalcemia are seen, including tetany and onvulsions. Chronically, neurological, ocular and cardiac deficiencies may also be seen. Hyperparathyroidism results in kidney stones and excessive demineralization, leading to weakening of bone.

Increases in PTH concentration in blood result in mobilization of calcium phosphate from the bone matrix, due primarily, and perhaps exclusively, to increased osteoplastic activity. Evidence of osteoplastic activity is reflected not only by calcium phosphate mobilization, but also by increased urinary excretion of hydroxyproline and other products of collagen breakdown.

In the kidney, PTH products three distinct effects, each of which contribution to the maintenance of calcium homeostasis. In the distal nephron PTH promotes the reabsorption of calcium, and in the proximal tubule it inhibits reabsorption of phosphate and promotes hydroxylation and hence activation of vitamin D.

Calcium balance ultimately depends on intestinal absorption of dietary calcium. Calcium absorption is severely reduced in hypo parathyroid patients and dramatically increased in those with hyperparathyroidism. PTH stimulates the renal enzyme that converts vitamin D to its active form, but has no direct effects on intestinal transport of either calcium or phosphate.

Regulation of PTH secretion:

Chief cells of the parathyroid glands are exquisitely sensitive to changes in extracellular calcium and rapidly adjust their rates of PTH secretion in a manner that is inversely related to the concentration of ionized calcium. The resulting increases or decreases in blood levels of PTH produce either positive or negative changed in the plasma calcium concentration and thereby provide negative feedback signals for regulation of PTH secretion. The activated form of vitamin D, the synthesis of which depends on PTH is also a negative feedback inhibitor of PTH synthesis.

The adrenal gland

These are two adrenal glands, one situated on the upper pole of each kidney enclosed within he **renal fascia**.

The glands are composed of two parts which have different structures & functions:

(1) Cortex:

To the outside, mesodermal in origin.

(2) Medulla:

In the center, originated from the ectodermal neural crest.

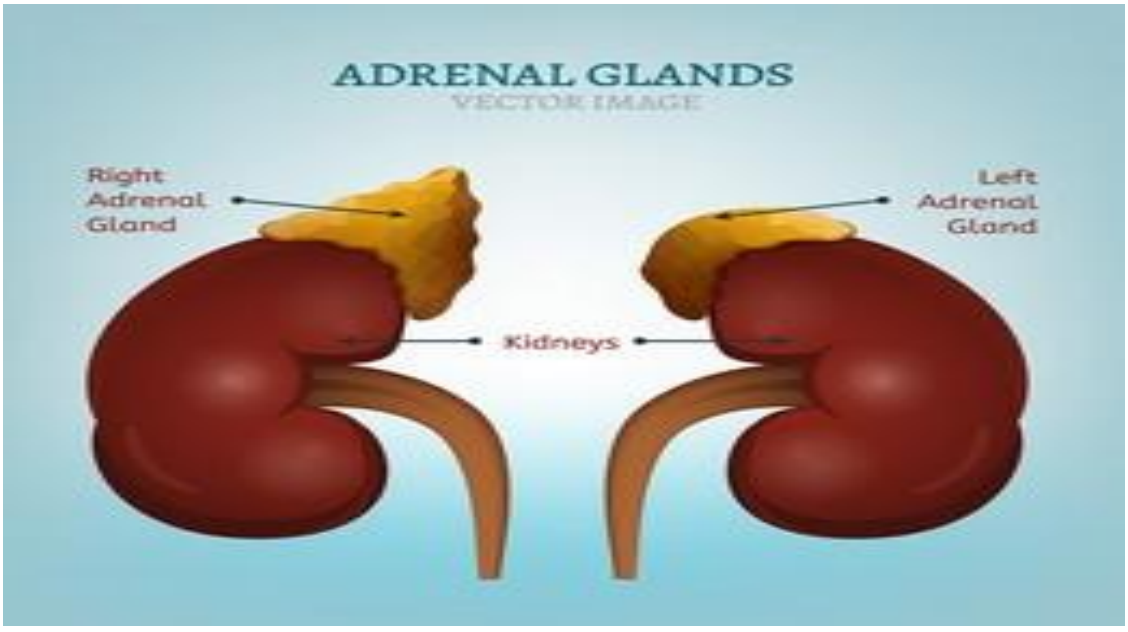
Thus it is not surprising that the 2 parts are under different control system & their products are completely different in structure &function.

Blood supply:-

The arterial blood supply to the glands is by branches from the abdominal aorta & renal arteries.

The venous return is y suprarenal veins:

- The right gland drains into the inferior vena cava & the left into the left renal vein.



(1)-Adrenal cortex

- The adrenal cortex produces three groups of **steroid hormones** from cholesterol.

- They are collectively called adrenocorticoids (corticosteroids, corticoids).
- They are glucocorticoids, mineralocorticoids & sex hormones (androgens).

-The cortex is divided into 3 distinct (zonae) parts:

(1) The zona glomerlusa, with secrete the ***steroid hormone, mineralocorticoids***.

(2) Zona fasciulata, which secrete ***glucocorticoids hormone***.

(3) Zona reticulosa, which produce ***the androgens (sex hormones)***.

The hormones in each group have different characteristic actions but due to their structures similarity their actions may overlap.

(1) The zona glomerulosa

- It is the outermost layer comprising 5-10 % of the cortex.
- The main mineralocorticoid that it secrets is aldosterone.
- **Its role is regulating sodium balance & blood pressure:**
  - It increases ***sodium reabsorption*** (promoting retention of sodium) by ***the renal tubules***.
  - Increase excretion of ***potassium & hydrogen atoms*** in the urine.
  - As a result, the osmotic pressure increases thus water is retained which elevates blood pressure by increasing blood volume.
  - Main site of action od aldosterone are ***the distal tubule & the collecting ducts in the kidney***.

Regulation of zona glomerulosa

- **Aldosterone is controlled by the :**
  a) Renin-angiotensin (RAS).
  b) Sodium &potassium.
  c) Hemorrhage.

(1) Decrease in blood pressure is detected detected by baroreceptors found in the arterial vessels of the kidney, resulting in release of ***renin***.

(2) ***Renin*** in a proteolytic enzyme, synthesized & stored within secretory granules in cells located at long the terminal part of ***the afferent arteriole*** entering the renal glomeruli called ***juxtaglomerular (JG)*** cells.

(3) Following stimulating of JG cells, ***renin*** is released into the blood where it act a plasma protein called ***angiotensinogen*** synthesized in liver, splitting off a decapeptide (10 amino acids) named ***angiotensin I***.

Angiotensinogen $\xrightarrow{\textit{Renin}}$ *Angiotensin I*

(4) A converting endopeptidase enzyme (***angiotensin converting enzyme ACE***) found in the endothelial cells (especially in the lung) quickly converts ***angiotensin I*** (by cleaving 2 more amino acids) to ***angiotensin II***.

Angiotensin I $\xrightarrow{\textit{ACE}}$ *Angiotensin II*

(5) Angiotensin II stimulates the cells of the adrenal zona glomerulosa aldosterone & is also a very to potent vasoconstrictor hormone.

(2) The zona fasciolata

It is the middle zone & is the thickest layer.

Cortisol (hydrocortisone), ***corticosterone*** & ***cortisone*** are the main glucocorticoids hormones.

Cortisol affects most tissues of the body & its effects are widespread.

Glucocorticoids are essential for ***life, regulating metabolism & response to stress,*** but most physiological effect of glucocorticoids is ***a metabolism*** (carbohydrates, protein& a lesser extent, fat).

Glucocorticoids have widespread effects & these include:

(1) ***Gluconeogenesis*** (formation of new sugar non-carbohydrate source e.g. protein) & ***hyperglycemia*** (raised blood glucose level).

(2) ***Lipolysis*** (breakdown of triglycerides into fatty acids & glycerol for energy production).

(3) Stimulating breakdown of protein, releasing amino acids which can be used for synthesis of proteins e.g. enzymes or for ATP production.

(4) Promoting absorption of sodium & water from renal tubules (***a weak mineralocorticoid effect***).

In pathological & pharmacological quantities glucocorticoids:

(5) Have anti-inflammatory action.

(6) Suppress the immune response.

(7) Delay wound healing.

(8) It affects as well as the cardiovascular gastrointestinal & skeletal systems.

Cortisol increases the concentration of glucose in the body by:

(1) Stimulating ***gluconeogenesis*** in the liver.

(2) Convert the increased blood glucose to glycogen in the liver.

(3) Decrease the utilization of glucose in other tissues.

(4) Enhances the breakdown of proteins in muscles & the release of amino acids necessary for ***gluconeogenesis*** in the liver.

(5) Mobilizes fatty acids from adipose tissue to the liver (***lipolytic action***) where their metabolism supply the energy required for ***gluconeogenesis***.

- Thus, although the action of this hormone in the lover is anabolic, the action on skeletal muscles & adipose tissue is ***catabolic***.
- The metabolic effects of cortisol (increased plasma concentration of glucose, amino acids &fatty) are ideally suited for adaptation to stress.
- Since foregoing food is associated with stress these metabolic changes are essential for survival during fasting.
- Also amino acids liberated by catabolism of protein stores not only provide a source of glucose but constitute of amino acids needed for tissue repair should injury occur.

Regulation of zona fasciculate

- The anterior pituitary controls the activity of zona fasciculate by adrenocorticotrophic hormone (***ACTH***) which stimulates the synthesis & release of cortisol.

- Cortisol has a direct ***negative feedback*** loop on the ***hypothalamus*** to influence the release of ***corticotrophin releasing hormone (CRH)***.
- Secretion of estradiol is also stimulated by stress.

(3) The zona reticularis

- It is the innermost layer &consists of cells which are similar to those of zona fasciculate.
- This zona secret **androgens**, although the production of androgens by the adrenal is minimal compared to their production by gonads.
- Their physiological role is still not clear.
- This zone is also regulated by ***ACTH***.

(II) The adrenal medulla

- The medulla is completely surrounded y the cortex.
- It develops from nervous tissue in the embryo &is part of the sympathetic division of the autonomic nervous system (i.e. ***originated from the ectodermal neural crest***).
- The adrenal medulla secrets 2 of hormones, ***adrenaline*** (epinephrine E) &***noradrenaline*** (norepinephrine NE).
- *Adrenaline, noradrenaline & dopamine* are collectively referred to as ***catecholamine***.
- The ***catecholamine*** is usually synthesized in ***the brain***, at synapse of postganglionic nerve ending & in ***the adrenal medulla***.
- Therefore they mayact as ***neurotransmitters*** or as ***neurohormones***.
- In the adult, ***adrenaline*** is the major product of the adrenal medulla constituting about ***80% of the catecholamines*** in the medulla &it is not synthesized in ***extramedullary tissue***.
- In contrast 20% only of noradrenaline is produced in the medulla, while it is primarily produced in neural tissues & released at the endings of sympathetic nerve fibers where it serves as neurotransmitter to carry signals across the gap that separates the fibers & the organ it innervates.
- The hormones of the adrenal medulla are not vital for survival.
- The hormones have been named the 3 F'S "fear-fight-flight" hormones because they contribute the response to stress.

- Due to the neural origin of the medulla it is closely related to the nervous system being innervated by preganglionic sympathetic fiber making is capable to respond instantaneously of stressful circumstances.
- The response involves stimulation of organ vital to the response (brain, muscle, cardiopulmonary stem & liver) at the express of other organs that are less immediately involved (skin, gastrointestinal & lymphoid systems).
- The adrenal medulla also synthesized &stores a number of ***opioidpeptide***, particularly ***met-enkephaline*** & ***leu-enkephalin*e**.
- The secretion of ***enkephaline*** from adrenal medulla may account for the ability of runners t overcome pain & production of ***a euphoric state*** over distance, through the action of ***endogenous analgesics***.

Regulation of secretion

- Stressful stimuli, whether negative or positive, activate certain nerve cells in the hypothalamus.
- These cells send signals to nerve cells in the spinal cord.
- The spinal cord cells extend to the adrenal medulla & stimulate it to release ***noradrenaline & adrenaline***.

Response of adrenal gland to stress

- When the body is under stress ***homeostasis*** is distributed.
- To restore it & in some cases to maintain life these are immediate & if necessary longer term response.
- Stressors include exercise, fasting, fright, temperature changes, disease & emotional disturbances situations.

The immediate response is sometimes descried as preparing for fight of flight; this is mediated by the sympathetic part of the autonomic nervous system &peripheral system.

The long-term response, ***ACTH*** from the anterior pituitary stimulates the release of glucocorticoids & mineralocorticoids from the adrenal cortex & a more prolonged response to stress occurs.

Actions of medullary hormones:

(1) On circulation: high dose of adrenaline or noradrenaline causes rise of both systolic and diastolic blood pressure. In small doses adrenaline slightly rises the systolic pressure, increases the heart rate and cardiac output. Adrenaline causes dilation of some blood vessels while constriction of others. Noradrenaline causes constriction of all vessels and thus causes ore rise of blood pressure.

(2) On respiration: adrenaline is more bronchodilator than noradrenaline. Adrenaline increases O_2 consumption by about 30% while noradrenaline has no such effect.

(3) On blood: adrenaline reduces the blood coagulation time. It increases the red cell count, hematocrit value, Hb concentration and plasma protein concentration. This may be due to movement of fluid out of the blood causing haemoconcentration. Adrenaline reduces the eosinophil count by about 50% in presence of corticoids.

(4) On metabolism: adrenaline stimulates glycogenolysis. It accelerates the breakdown of glycogen in liver into glucose in blood and also affects the conversion of muscle glycogen into lactic acid. Adrenaline also stimulates the secretion of ACTH. The discharge of glucocorticoids is increased and gluconeogenesis is stimulated.

The Pancreatic Islets

The principle pancreatic hormones are insulin and glucagon, whose opposing effects on the liver regulate hepatic storage, production, and release of energy rich fuels.

Insulin is an anabolic hormone that promotes sequestration of carbohydrate, fat, and protein in storage depots throughout the body. Its powerful actions are exerts principally on skeletal muscle, liver and adipose tissue, whereas those of glucagon are restricted to the liver, which respond by forming and secreting energy-rich water-soluble fats: glucose, acetoacetic acid and Beta-hydroxybutric acid.

Glucagon acts in concert with other fuel-mobilizing hormones to counter balance the fuel0storing effects of insulin.

Because compensatory changes in secretion of all of these hormones are readily made, states of glucagon excess or deficiency rarely lead to overt human disease. Insulin, on the other hand, acts alone, and prolonged survival is not possible in its absence. Inadequacy of insulin due either to insufficient production [diabetes mellitus type I; insulin-dependent diabetes mellitus (IDDM)] or end-organ unresponsiveness [diabetes mellitus type II; noninsulin-dependent diabetes mellitus (NIDDM)] results in one of the most common of the endocrine diseases affecting more than 3% of the American population.

Morphology of the endocrine pancreas:

The 1-2 million islets of the human pancreas range in size from about 50 to about 500 mm in diameter. Collectively the islets comprise only 1-2% of the pancreatic mass.

Blood is supplied by the pancreatic artery and drains into the portal vein, which thus delivers the entire output of pancreatic hormones to the liver. The islets are also richly innervated with both sympathetic and parasympathetic fibers that terminate on or near the secretory cells.

Histologically, the islets consist of three cells types **beta cell**. Which synthesize and secrete insulin make up about 60-75% of a typical islets. **Alpha cells** are the source of glucagon and comprise perhaps as much as 20% of islet tissue. **Delta cells**, which are considerably less abundant, produce somatostatin.

An additional but rarer cell type, the **F cell** may also appear in the exocrine part of the pancreas. A fifth cell type that secrets ghrelin has been identified recently in both fetal and adult islets.

1- GLUCAGON

Biosysnthesis, secretion and metabolism:

Glucaogon is a simple unbranched peptide chain that consists of 29 amino acids and has a molecular weight of about 3,500. Its amino acid sequence has been remarkably preserved throughout evolution of the vertebrates.

The glucagon gene, which is located on chromosome 2, is expressed primarily in the alpha cell, L-cell of the intestinal epithelium, and discrete brain areas. It encodes a large, 158-amionacide preprolucagon protein that is processed in a tissue-specific manner to give rise to at least six biologically active peptides that contain similar amino acid sequences. In alpha cells, the preprologlucagon molecule is enzymatically cleaved to release glucagon and the major proglucagon fragment.

Glucagon is packaged, stored in membrane-bound granules, an secreted by exocytosis like other peptide hormones. It circulates without binding to carrier proteins and has-life in blood in blood of about 5 minutes.

Glucagon concentrations in peripheral blood are considerable lower than in portal venous blood. This difference refers the fact that about 25% of the secreted glucagon is destroyed during passage through the liver. The kidney is another important site of degenerated and a considerable fraction of circulating glucagon is destroyed by plasma peptidases.

Physiological actions of glucagon:

The physiological role of glucagon is to stimulate hepatic production and secretion of glucose and to a lesser extent, ketone bodies that are derived from fatty acids. Under normal circumstances, liver and possible pancreas beta cells are the only target of glucagon action.

Glucagon stimulates the liver to release glucose and produces a prompt increase in blood glucose concentration. Glucose that is released from the liver is obtained from breakdown of stored glycogen (glycogenolysis) and from new synthesis (gluconeogenesis). Because the

principle precursors for gluconeogenesis are amino acids, especially (alanine, glucagon also increases hepatic production of urea (ureogenesis) from the amino groups.

Glucagon also increase production of ketone bodies (ketogenesis) by directing metabolism of long-chain fatty acids toward oxidation and away from esterification and export as lipoproteins. Concomitantly, glucagon also promote breakdown of hepatic triglycerides to yield long-chain fatty acids, which, along with fatty acids that reach the liver from peripheral fat depots, provide the substance for ketogenesis.

All of the effects of glucagon appear to mediated y cyclic AMP. Glucagon may also increase intracellular concentrations of calcium by a mechanism that depends on activation of protein kinase A, and the increased calcium may reinforce some actions of glucagon, particularly on glycogenolysis.

Regulation of glucagon secretion:

The concentration of glucose in blood is the most important determinant of glucagon secretion in normal individuals. When the plasma glucose concentration exceeds 200mg/dl, glucagon secretion is maximally inhibited. Inhibitory effects of glucose are proportionately less at lower concentrations and disappear when glucose concentration falls below 50 mg/dl.

The set point for glucose concentration thus falls well within the range over which glucagon secretion is regulated, and alpha cells can be respond to changes in blood appear to respond directly to changes in glucose concentration, but we do not yet understand how they monitor blood glucose concentration and translate that information to an appropriate rate of glucagon secretion.

Low blood glucose (hypoglycemia) not only relieves inhibition of glucagon secretion, but this life-threatening circumstance stimulates the central nervous system to single both parasympathetic and sympathetic nerve ending within the islet to release their neurotransmitters, acetylcholine and vasoactive intestinal peptide from parasympathetic endings, and norepinephrine and neuropeptide Y (NPY) from sympathetic endings.

Alpha cells express receptors for these neurotransmitters, and they secrete glucagon in response to both parasympathetic and sympathetic stimulation.

Glucagon secretion is evoked by a meal rich in amino acids. Alpha cells respond directly to increased blood levels of certain amino acids, particularly arginine.

2-INSULIN

Biosynthesis, secretion and metabolism:

Insulin is composed of two unbranched peptide chains joined together by two disulfide bridges. The singles gene that encodes the preproinsulin molecule consists of three exons and two introns and two introns and is located on chromosome 11.

After removal of leader sequence in ER the pro insulin molecule undergoes folding and disulphide bond formation before it is transferred to Golgi apparatus where it is packaged in secretory granules and stored complexed with zinc.

Processing of the single chain pro insulin molecule to form the two chained mature insulin takes place in the secretory granules where 31-residue peptide, called the connecting peptide (C peptide), is excised by stepwise actions of two trypsin like enzymes called *prohormone convertases*.

When insulin is secreted, the entire contents of secretory vesicles are disgorged into extracellular fluid. Consequently, the C peptide and any remaining proinsulin and processing intermediates are released into circulation.

Insulin is cleared rapidly from the circulation with a half-life of 4-6 minutes and is destroyed by a specific enzyme, called (insulinase) (or insulin-degrading enzyme), that is present in liver, muscle, kidney and other tissues.

The first step in insulin degrading is receptor-mediated internalization through an endosome mechanism. Degradation may take place within endosomes or after fusion of endosomes with lysosomes. The liver is the principal site of insulin degradation and inactivates about 30-70% of the insulin that reaches it in hepatic portal blood.

The kidneys destroy about half of the insulin reaches the general circulation following receptor-mediated uptake, both from the glomerular filtrate and from post glomerular blood plasma. Muscle and other insulin-sensitive tissues through the body apparently account for destruction of the remainder.

Because little degradation of the C peptide occurs in the liver, its concentration in blood is useful for estimating the rate of insulin secretion and for evaluation of beta cell function in patients who are receiving injection of insulin.

Physiological actions of insulin:

The actions of insulin on the global human metabolism level include:

1- Control of cellular intake of certain substances, most prominently glucose in muscle and adipose tissue (about 2/3 of the body cells).
2- Increase of DNA replication and protein synthesis via control of amino acid uptake.
3- Modification of the activity of numerous enzymes.

The actions of insulin on cells include:

I. Increased glycogen synthesis –insulin forces storage of glucose in liver (and muscle) cells in the form of glycogen, lowered levels of insulin cause liver cells to convert glycogen to glucose and excrete it into the blood. This is the clinical action of insulin, which is directly useful in reducing high blood glucose levels as in diabetes.
II. Increased fatty acid synthesis-insulin forces fat cells to take in blood lipids, which are converted to triglycerides; lack of insulin causes the reverse.
III. Increased esterification of fatty acids-forces adipose tissue to make fats (i.e., triglycerides) from fatty acid esters: lack of insulin causes the reverse.
IV. Decreased proteolysis-decreasing the breakdown of protein.
V. Decreased lipolysis-forces reduction in conversion of fat cell lipid stores into blood fatty acids; lack of insulin causes the reverse.
VI. Decreased gluconeogenesis – decreases production or glucose from non-sugar substrates, primarily in the liver (remember, the vast majority of endogenous insulin arriving at the liver never leaves the liver), lack of insulin causes glucose production from assorted substrates in the liver and elsewhere.
VII. Increased amino acid uptake-forces cells to absorb circulating amino acids, lack of insulin inhibits absorption.

Regulation of insulin secretion:

As might be expressed of a hormone whose physiological role is promotion of fuel storage, insulin secretion is greater immediately after eating and decreases during between meal periods. Coordination of insulin secretion with nutritional state as well as with fluctuating demands of energy production is achieved through stimulating of beta cells by metabolites, hormones and neural signals.

Glucose is the most important regular of insulin secretion. In the normal individual its concentration in blood is maintained within the narrow range of about 70-80 mg/dl after an overnight fast to about 150 mg/dl immediately after a glucose-rich meal. When blood glucose increases above a threshold value, insulin secretion increases proportionately. At low concentrations, adjustments in insulin secretion are largely governed by other stimuli that act as amplifiers or inhibitors of the effects of glucose.

Amino acids are important stimuli for insulin secretion. The transient increase in plasma amino acids after a protein-rich meal is accompanied by increased secretion of insulin. Arginine, lysine and leucine are the most potent amino acid stimulators of insulin secretion.

Secretion of insulin in response to blood intake is also mediated by a neural pathway. The taste or smell of food or the expectation of eating increase insulin secretion during this so-called *cephalic phase* of feeling.

An increase in the concentration of glucose in portal blood is detected by glucose sensors in the wall of the portal vein and the information is relayed to the brain via vagal afferent nerves. In response, vagal efferent nerves stimulates the pancreas to secrete insulin and the liver to take up glucose.

3-Somatostatin (GHRIH)

- In pancreas somatostatin is synthesized by the D-cells,
- Since it was identifies in the hypothalamus & it inhibit release of growth hormone from pituitary gland.
- Somatostatin has also been identifies in a number of tissues including many areas of the brain, gastrointestinal tract & the pancreas.
- Generally somatostatin is an inhibitory pancreas hormone & in the pancreas it inhibits the release of both insulin & glucagon.
- The hormone has been implicated in the regulation of nutrient-concentration in the exaggerated response following a meal.

- It has been found to retard the entry of nutrient into the body by inhibiting various digestive digestive events ***such as***:
  (1) Gastric emptying.
  (2) Acid secretion.
  (3) Pepsin & gastrin secretion.
  (4) Duodenal motility.
- So the function of somatostatin hormone is regulating the movement of the nutrient from the gut to the internal environment.

4- <u>Pancreatic polypeptide (PP):</u>

- It is a peptide found in the F-cells of the islets of Langerhans of the pancreas.
- PP is released after a high portion meal& in the case of hypoglycemia.
- Its major effect is the inhibition of the secretion of enzymes by the pancreas & the bile by the gall bladder.

<u>5-Amylin:</u>

- Recent literature reveals that peptide is secreted from beta-cells of the pancreas that secret insulin.
- Although it is co-secreted with insulin, in response to glucose & other beta-cells stimulators, it was found to have opposing metabolic effects to those of insulin.
- It metabolic role is unclear.

Structure / Cells	Hormone	Primary Targets	Hormonal Effects	Regulatory Control
Pancreatic islets				
Alpha cells	Glucagon	Liver, adipose tissues	Mobilizes lipid reserves; promotes glucose synthesis and glycogen breakdown in liver; elevates blood glucose concentrations	Stimulated by low blood glucose concentrations; inhibited by somatostatin from delta cells
Beta cells	Insulin	Most cells	Facilitates uptake of glucose by target cells; stimulates lipid and glycogen formation and storage	Stimulated by high blood glucose concentrations, parasympathetic stimulation, and high levels of some amino acids; inhibited by somatostatin from delta cells and by sympathetic activation
Delta cells	Somatostatin (GH-IH)	Other islet cells, digestive epithelium	Inhibits insulin and glucagon secretion; slows rates of nutrient absorotion and enzyme secretion along digestive tract	Stimulated by protein-rich meal; mechanism uncertain
F cells	Pancreatic polypeptide	Digestive organs	Inhibits gallbladder contraction; regulates production of pancreatic enzymes; influences rate of nutrient absorption by digestive tract	Stimulated by protein-rich meal and by parasympathetic stimulation

Reproductive endocrinology

- Is the study of endocrine physiology of male & female reproductive system.
- The hormones of the male & the female play an important role in the differentiation, growth & maintenance of the sexual reproductive tissue necessary for continuation of the species.

Male reproductive system:

It consists of the two testes, epididymis, vas deference, the ejaculatory duct in addition of the male accessory glands which include prostate, seminal vesicles and two urethral glands.

Function of the male gonads(testis):

1- Synthesis of the male sex hormones (androgens).
2- The production of gametes (spermatogenesis).

The androgens

- These are hormones vital for development & functioning of the male reproductive systems.
- The *Ledig cells* found between the seminiferous tubules in the testes secrete a number of *androgens* which include a large amount testosterone & small quantity of *progesterone*.
- Testosterone is converted to the more potent androgens (Dihydrotestosterone "DHT") in many target cells.
- Also testosterone changes to estradiol in the tissue.
- The role of estradiol & progesterone in the male not clear.
- The secreted testosterone is mostly bound to plasma proteins, either albumin or beta-globulin called sex hormone binding globulin ***(SHBC)***.

Action of androgens:

1-Testosterone is vital for completion of spermatogenesis I the seminiferous tubules.
2-Androgens are necessary for the appearance & development of male 2ry sex characteristics.
3-Androgens are strong anabolic hormones responsible for the male muscular development & greater growth rate.

4-Androgens stimulate growth of facial & body hair, recession of scalp hair & thickening of voice.

5-They are responsible for male sex "drive" & behavioral development.

Control of androgen production:

- The synthesis & secretion of testosterone & spermatogenesis is controlled by a gonadotrophin releasing hormone ***(GnRH)***from the hypothalamus that stimulates *gonadotrophe cells* of the anterior pituitary to secrete both follicle stimulating hormone ***(FSH)*** & luteinizing hormone ***(LH)***.
- Testosterone acts on the hypothalamus to decrease secretion of ***GnRH***.

Female reproduction system:

It consists of the 2 ovaries, fallopian tubes (oviducts), uterus & vagina (birth canal).

The function of the female gonad (ovary) is:

1-Biosynthesis & secretion of the female sex hormone ***progesterone & estrogen***.

2-Production of gametes (***oogenesis***).

Ovarian hormones:

1-Estrogen are group steroid hormone that have similar effects on femal reproductive system Estradiol being the major estrogen secreted by ***the Graafian follicle*** in the ovaries.

2-Progesterone is another steroid hormone secreted by ***the corpus leutum & by the placenta*** during pregnancy.

3-Ovary also produces 2 peptide hormones inhibin & relaxin.

(a)***Inhibin*** inhibits the production of FSH from the anterior pituitary.

(b)***Relaxin*** helps during childbirth.

4-The relative amount of the ovarian hormones secreted ***vary*** throughout ***the menstrual cycle*** & drastically in ***the prequantstate***.

5-When released into circulation, the gonadal steroid bind to plasma proteins, estradiol to sex hormone binding globulin (***SHBG***), while progesterone bind to cortico-steroid binding globulin (***CBG***).

Action of Estrogens:

They are responsible for inhibiting & maintaining maturity of the female genitalia & 2ry sex characteristics.

1- Stimulate ovary & follicle growth as well as reproductive tract.
2- Stimulate external genitalia.
3- Stimulate breast growth.
4- Stimulate female body configuration development: marrow scolders, broad hips & female pubic hair.
5- Stimulate the rapid union of growth center of bones, epiphysis with the shafts of the long bones that is what the growth of girls ceases earlier than the boys.
6- Affect the epithelium of the skin, causing it to become soft & smooth.
7- Cause deposition of subcutaneous adipose tissue & are responsible for the characteristics distribution of fat in the mature female.
8- Together with progesterone, they maintain * control the normal menstrual cycle.

Action of progesterone:

- The main effects of progesterone are the preparation the endothelium for implantation & maintenance of pregnancy.
    1- It causes the secretory changes necessary for implantation of the fertilized ovum & it suppresses uterine contractions.
    2- It has a profound effect on the fluid balance causing the kidneys to retain water * the tissues to accumulate fluids.
    3- Stimulate breast growth, particularly glandular tissue.
    4- During pregnancy it is responsible for inhibition of ovulation.

Control of ovarian hormones:

- The basic factors contrloing the production of the ovarian hormones are similar to those described for testicular function I that they involve:
    a) ***GnRH*** from hypothalamus.
    b) The anterioir pituitary gonadotrophin (***LH & FSH***).
    c) The gonadal sex hormones (***estrogen & progesterone***).
- However, in the female the amount of **GnRH** secreted from the hypothalamus is cyclic, the female sex hormones changes over the course of menstrual cycle due to the development of the ovum.
- The interaction of the sex hormones & hypothalamus-pituitary hormones in the female is very complex & variable.
- Throughout most of the menstrual cycle, ovarian steroids exert a negative feedback effect of both secretion of both ***FSH & LH***.
- During the second half of the follicular phase, estradiol exerts a positive feedback effect resulting in an increase in gonadotropins especially LH.

Menstrual cycle

- The menstrual cycle may be derived into two main phases that are nearly equal in length:

1- **The follicle phase:** during which a single mature follicle develops forming the ***Graafian follicle & end by ovulation***.

1.a- At the beginning of each menstrual cycle several oocyte are found growing in the ovary.

1.b- About a weak into the cycle a selection occurs & ***only one secondary oocyte*** is chosen, the ***dominant follicle*** & continues to develop while the others that had begun to enlarge during that week degenerate.

1.c- The dominant follicle matures & is called ***the Graafian follicle***.

1.d- ***Ovulation*** occurs when the wall of the follicle & the ovary rapture & the oocyte is expelled out of the ovary into the ***fallopian tubes*** (oviduct).

2- **The luteal phase:** beginning after ovulation & formation of the corpus luteum (CL) & ends by the degeneration of the CL & ovum.

2.a- After the Graafian follicle discharges its ovum, it undergoes rapid transformation, where the cells enlarged greatly & a gland known as the corpus luteum formed.

2-b- If the ovum in the oviduct is not fertilized within two days , the corpus luteum degenerates.

2.c- The disappearance of the corpus luteum leads to menstruation & a new cycle begins.

Hormonal regulation of the menstrual cycle:-

1-At the end of the cycle plasma estrogen conc. is low exerting little negative feedback inhibition on the hypothalamus & anterior pituitary thus GnRH increases stimulating FSH & LH secretion.

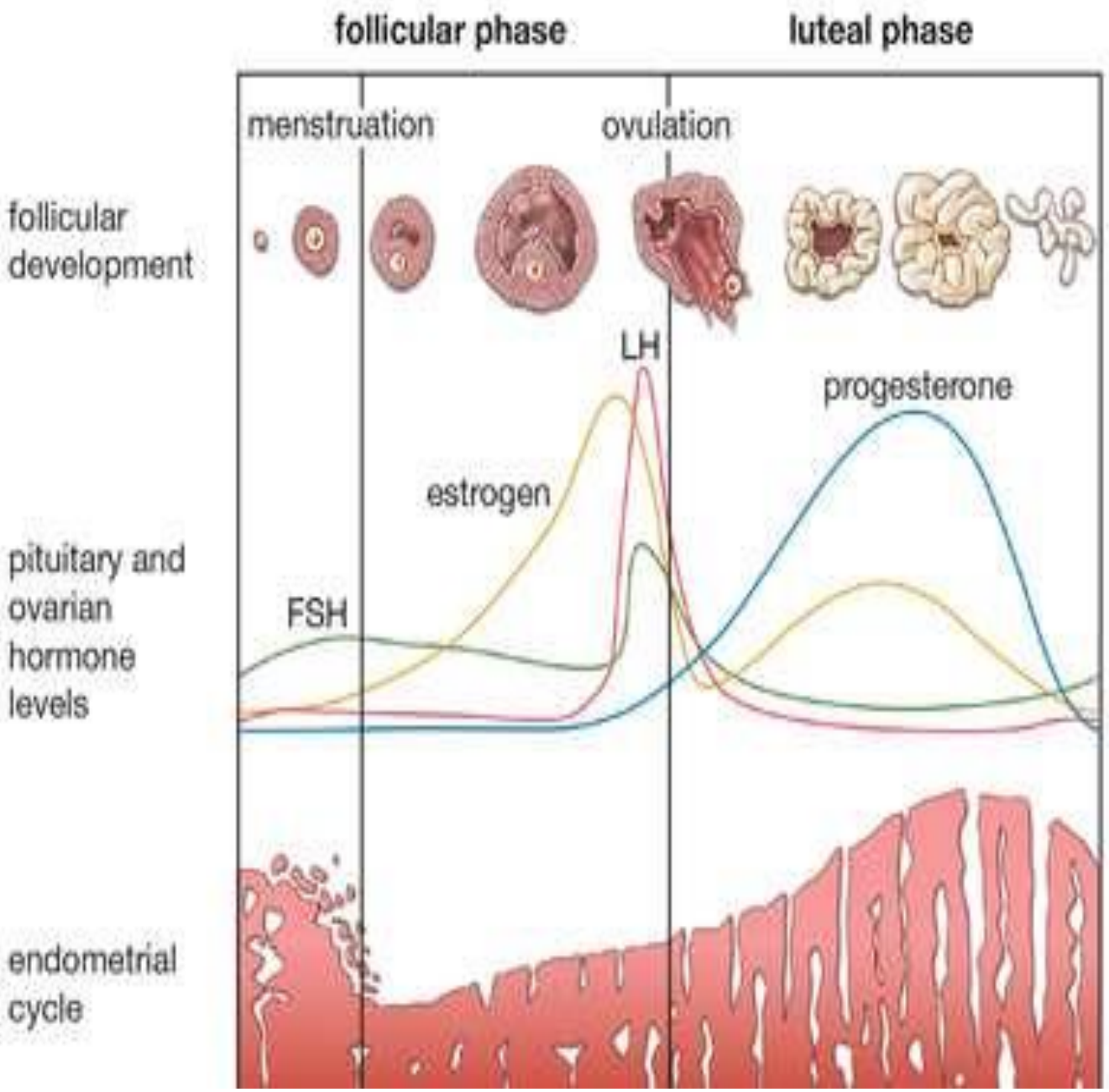
2-Under the effect of rising level of FSH & LH the follicle develop.

3-The follicle ***produce estrogen*** & the end of the 1st week the selected dominant follicle becomes the major produce of estrogen, markedly increasing plasma estrogen levels.

4-The increase level of estrogen exerts a ***negative feedback*** inhibition on ***GnRH, FSH & LH*** levels that gradually decrease in plasma.

5- During the late follicle phase (days 11,12 & 13 of the cycle), plasma estrogen level ***rises*** dramatically due to enlarged Graafian follicle & decrease level of gonadotropins (***GnRH, FSH & LH***).

6- The raised estrogen levels, if maintained high for a minimum period of 36 hours, has a positive effect on the hypothalamoanteroir pituitary system; consequently there is a sudden rapid increase (called surge) in LH & FSH secretion, this surge of gonadotropins induces the follicle to rapture & ovulation occurs.


follicular phase
luteal phase
menstruation
ovulation
follicular development
LH
progesterone
estrogen
pituitary and ovarian hormone levels
FSH
endometrial cycle

Structure/cells	Hormone(s)	Primary Targets	Hormonal Effects	Regulatory Control
Testes				
Interstitial cells	Androgens	Most cells	Support functional maturation of sperm, protein, synthesis in skeletal muscles, male secondary sexual characteristics, and associated behaviors	Stimulated by LH from anterior pituitary gland (see figure 18-10a)
Ovaries				
Follicular cells	Estrogens	Most cells	Support follicle maturation, female secondary sexual characteristic, and associated behaviors	Stimulated by FSH and LH from anterior pituitary gland see figure (18-10a)
	Inhibin	Anterior pituitary gland	Inhibits secretion of FSH	Stimulated by FSH from anterior pituitary gland (see figure 18-10a)
Corpus luteum	Progestins	Uterus, mammary gland	Prepare uterus for implantation; prepare mammary glands for secretory activity	Stimulated by LH from anterior pituitary gland (see figure 18-10a)
	Relaxin	Pubic symphysis, uterus, mammary glands	Loosens pubic symphysis, relaxes uterine (cervical) muscles, stimulates mammary gland development	Stimulated by LH from the anterior pituitary gland and by placental hcG (human chorionic gonadotropin)

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