LABORATORY ACTIVITY PHYSIOLOGY

Resource Person : Widayanti,dr., M.Kes
Subject : Physiology of Neurotransmitter and Motoric Nervous System
Department : Physiology

A	**SEQUENT**			
	I	Introduction	:	30 menit
	II	Pretest	:	5 menit
	III	Laboratory activity	:	110 menit
	IV	Post test	:	
B	**TOPIC**			
	Date: October 8th 2019			
	1. Discussion about Physiology of Synaps and Neurotransmitter 2. Discussion about Physiology of Motoric Nervous System		: :	50 menit 60 menit
C	**VENUE**			
	Biomedical Laboratory, Faculty of Medicine, Unisba, Jl. Tamansari No.22 Bandung 40116			
D	**EQUIPMENT**			
	1	Discussion about Synaptic Potential, and Synaptic Transmission, and Neurotransmitter Action on Ion Channel at Nervous System	a. Laptop b. Software Interactive Physiology Adam Benjamin Cummings c. Software Physio-ex d. Projector	
	2	Discussion about physiology of direct motoric pathway	Posters	
	3	Discussion about physiology of indirect motor pathway	Posters	
	4	Discussion about physiology of cerebellum and basal ganglia in Motoric System	Posters	
E	**TASK**			
	At the end of the activity the students will understand and can describe about: 1. synaptic Potential and Synaptic Transmission 2. neurotransmitter release and action at receptor in nervous system 3. direct motor pathway and its function 4. indirect motor pathway and its function 5. basal ganglia pathway and its function			
F	**IMPLEMENTATION**			
	1. Students are divided into 18 groups 2. Each group is supervised by one tutor			

Activity 1 : Synaptic Potential, Synaptic Transmission and Neurotransmitters

The synapse is the junction point from one neuron to the next. Synapses determine the directions that the nervous signals will spread through the nervous system.

Nerve impulse (1) may be blocked in its transmission from one neuron to the next,

(2) may be changed from a single impulse into repetitive impulses, or (3) may be integrated with impulses from other neurons to cause highly intricate patterns of impulses in successive neurons.

There are 2 major types of synapses: (1) the *chemical synapse* and (2) the *electrical synapse*. Almost all the synapses used for signal transmission in the CNS of the human being are *chemical synapses*. In these, the first neuron secretes at its nerve ending synapse a chemical substance called a *neurotransmitter* and this transmitter in turn acts on receptor proteins in the membrane of the next neuron to excite the neuron, inhibit it, or modify its sensitivity in some other way. Some of neurotransmitters are acetylcholine, norepinephrine, epinephrine, histamine, gamma-aminobutyric acid (GABA), glycine, serotonin, and glutamate.

Electrical synapses are characterized by direct open fluid channels that conduct electricity from one cell to the next. Most of these consist of small protein tubular structures called *gap junctions* that allow free movement of ions from the interior of one cell to the interior of the next. Only a few examples of gap junctions have been found in the central nervous system.

Chemical synapses always transmit the signals in one direction: that is, from the neuron that secretes the transmitter substance, called the *presynaptic neuron*, to the neuron on which the transmitter acts, called the *postsynaptic neuron*. This is the *principle of one-way conduction.* It is quite different from conduction through electrical synapses, which often transmit signals in either direction. The extreme importance of the one-way conduction mechanism. It allows signals to be directed toward specific goals.

Transmitter Release from the Presynaptic Terminals

Presynaptic membrane contains large numbers of *voltage-gated calcium channels*. When an action potential depolarizes the presynaptic membrane, these calcium channels open and allow large numbers of calcium ions to flow into the terminal. The quantity of transmitter substance that is then released from the terminal into the synaptic cleft is directly related to the number of calcium ions that enter.

When the calcium ions enter the presynaptic terminal, they bind with special protein molecules on the inside surface of the presynaptic membrane, called *release sites*. This binding in turn causes the release sites to open through the membrane, allowing a few transmitter vesicles to release their transmitter into the cleft after each single action potential.

Action of the Transmitter Substance on the Postsynaptic Neuron

The membrane of the postsynaptic neuron contains large numbers of *receptor proteins*. The molecules of these receptors have 2 important components:

1. a *binding component* that protrudes outward from the membrane into the synaptic cleft.It binds the neurotransmitter coming from the presynaptic terminal
2. an *ionophore component* that passes all the way through the postsynaptic membrane to the interior of the postsynaptic neuron.

The ionophore in turn is one of two types:

1. an *ion channel* that allows passage of specified types of ions through the membrane or
2. a *"second messenger" activator* that is not an ion channel but instead is a

molecule that protrudes into the cell cytoplasm and activates one or more substances inside the postsynaptic neuron. These substances in turn serve as "second messengers" to increase or decrease specific cellular functions.

Ion Channels

The ion channels in the postsynaptic neuronal membrane are usually of two types:

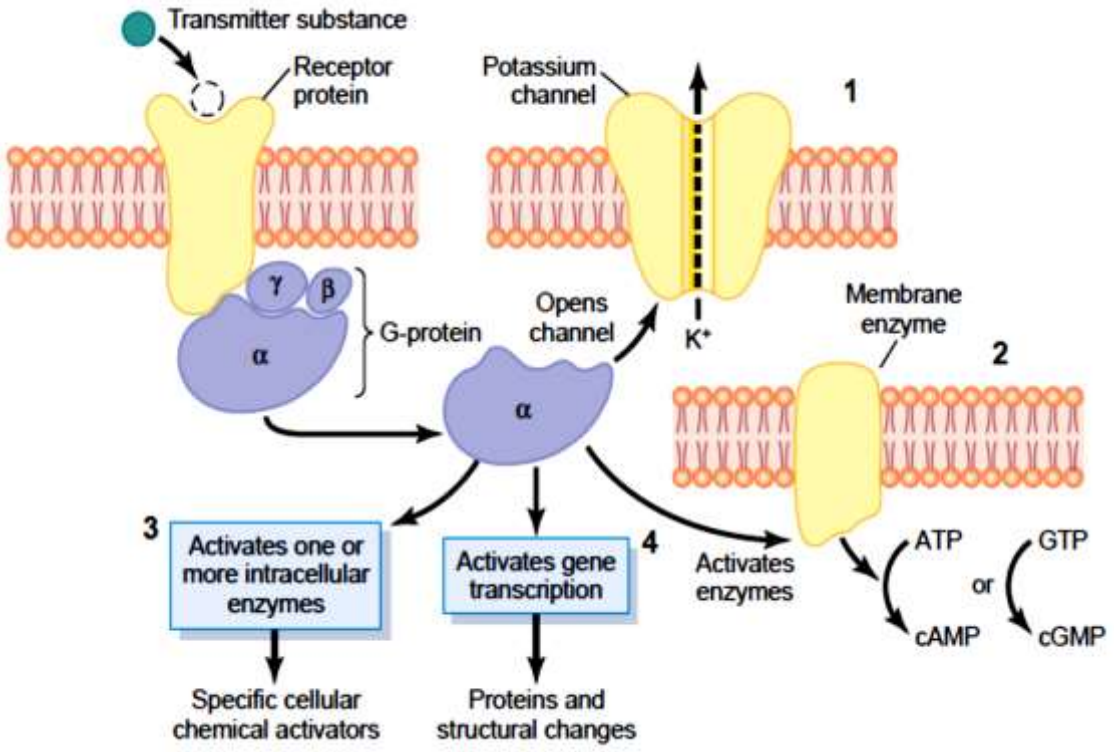
1. *cation channels* that most often allow sodium ions to pass when opened, but sometimes allow potassium and/or calcium ions as well,
2. *anion channels* that allow mainly chloride ions to pass but also minute quantities of other anions

A transmitter substance that opens cation channels is called an *excitatory transmitter*. Conversely, transmitter substances that open anion channels allows negative electrical charges to enter neuron are called *inhibitory transmitters.*

Many functions of the nervous system, such as memory, require prolonged changes in neurons for seconds to months after the initial transmitter substance is gone.The ion channels are not suitable for causing prolonged postsynaptic neuronal changes. prolonged postsynaptic neuronal excitation or inhibition is achieved by activating a "second messenger" chemical system inside the postsynaptic neuronal cell itself, and then it is the second messenger that causes the prolonged effect. One of the most common types uses a group of proteins called *G-proteins*.

A G-protein is attached to the portion of the receptor that protrudes into the interior of the cell. The G-protein in turn consists of three components: an alpha (α) component that is the *activator* portion of the G-protein, and beta (β) and gamma (γ) components that are attached to the alpha component and also to the inside of the cell membrane adjacent to the receptor protein. On activation by a nerve impulse, the alpha portion of the G-protein separates from the beta and gamma portions and then is free to move within the cytoplasm of the cell. Inside the cytoplasm, the separated alpha component performs one or more of multiple functions, depending on the specific characteristic of each type of neuron. They are:

1. *Opening specific ion channels through the postsynaptic cell membrane*
2. *Activation of cyclic adenosine monophosphate(cAMP) or cyclic guanosine monophosphate(cGMP) in the neuronal cell*. Cyclic AMP or cyclic GMP can activate highly specific metabolic machinery in the neuron and can initiate any one of many chemical results, including long-term changes in cell structure itself, which in turn alters long-term excitability of the neuron.
3. *Activation of one or more intracellular enzymes*. In turn the enzymes can cause any one of many specific chemical functions in the cell.
4. *Activation of gene transcription. G*ene transcription can cause formation of new proteins within the neuron, thereby changing its metabolic machinery or its structure, especially in long-term memory processes.



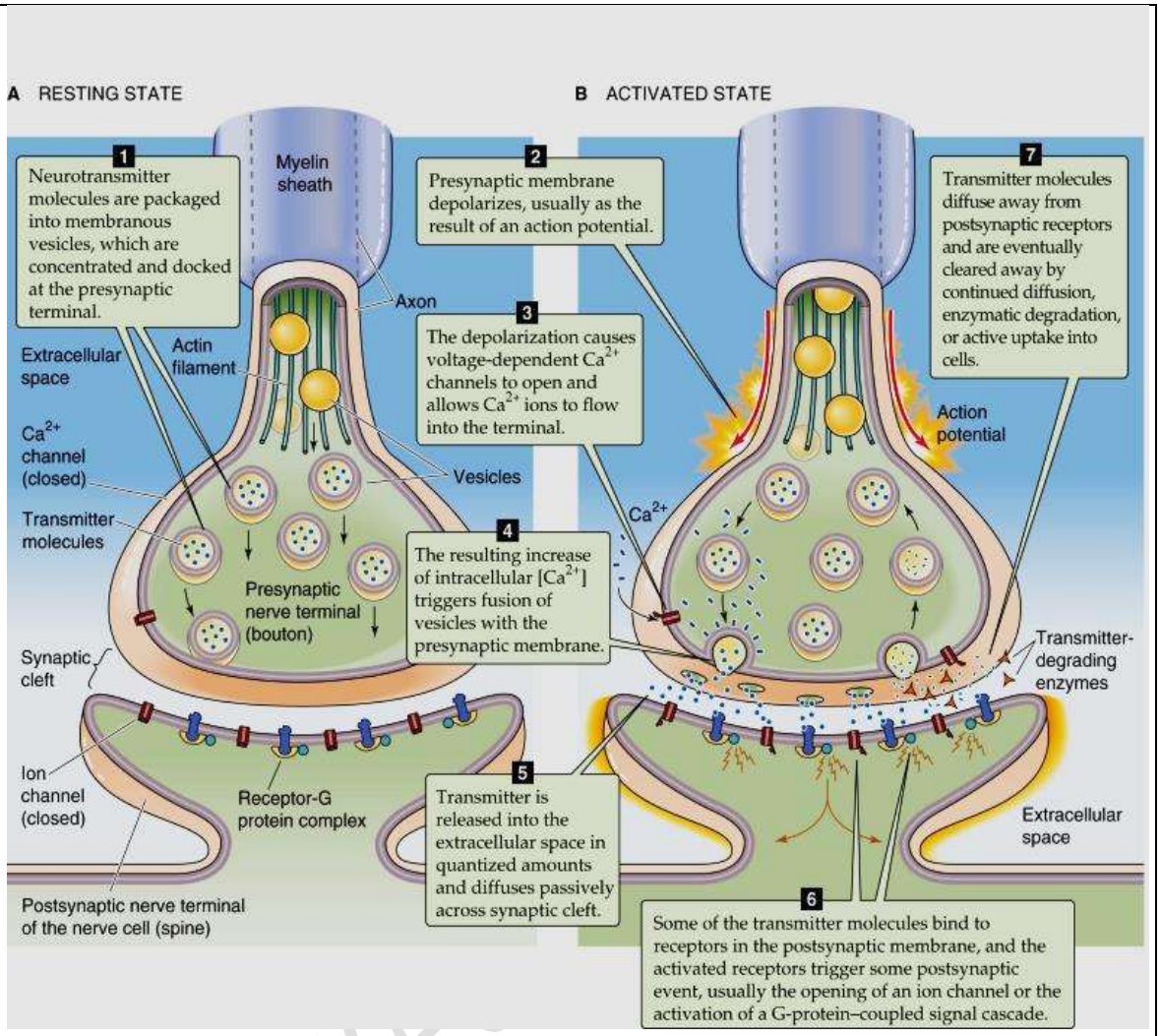
Excitatory or Inhibitory Receptors in the Postsynaptic Membrane

Excitation

1. *Opening of sodium channels allow large numbers of positive electrical charges to flow to the interior of the postsynaptic cell*.
2. *Depressed conduction through chloride or potassium channels, or both*.
3. *Various changes in the internal metabolism of the postsynaptic neuron* to excite cell activity or, in some instances, to increase the number of excitatory membrane receptors or decrease the number of inhibitory membrane receptors.

Inhibition

1. *Opening of chloride ion channels through the postsynaptic neuronal membrane*.
2. *Increase in conductance of potassium ions out of the neuron*.
3. *Activation of receptor enzymes* that inhibit cellular metabolic functions that increase the number of inhibitory synaptic receptors or decrease the number of excitatory receptors



Synaptic Transmitters

Two groups of synaptic transmitters :

1. *Small-molecule, rapidly acting transmitters*.
2. *Neuropeptides* of much larger molecular size that are usually much more slowly acting.

The small-molecule, rapidly acting transmitters are the ones that cause most acute responses of the nervous system, such as transmission of sensory signals to the brain and of motor signals back to the muscles.

The neuropeptides, in contrast, usually cause more prolonged actions, such as long-term changes in numbers of neuronal receptors, long-term opening or closure of certain ion channels, and possibly even longterm changes in numbers of synapses or sizes of synapses.

Small-Molecule Transmitters

Acetylcholine

Acetylcholine is secreted by neurons in many areas of the nervous system but specifically by :

(1) the terminals of the large pyramidal cells from the motor cortex
(2) several neurons in the basal ganglia
(3) the motor neurons that innervate the skeletal muscle

(4) the preganglionic neurons of the autonomic nervous system
(5) the postganglionic neurons of the parasympathetic nervous system
(6) some of the postganglionic neurons of the sympathetic nervous system.
In most instances, acetylcholine has an excitatory effect; however, it is known to have inhibitory effects at some peripheral parasympathetic nerve endings, such as inhibition of the heart by the vagus nerves.

Norepinephrine
Norepinephrine is secreted by the terminals of many neurons whose cell bodies are located in the brain
stem and hypothalamus. Specifically, norepinephrine secreting neurons located in the *locus ceruleus* in the
pons send nerve fibers to widespread areas of the brain to help control overall activity and mood of the mind, such as increasing the level of wakefulness. In most of these areas, norepinephrine probably activates excitatory receptors.

Dopamine
Dopamine is secreted by neurons that originate in the substantia nigra.The termination of these neurons
is mainly in the striatal region of the basal ganglia.The effect of dopamine is usually inhibition.

Glycine
Glycine is secreted mainly at synapses in the spinal cord. It is believed to always act as an inhibitory
transmitter.

GABA
GABA (*gamma-aminobutyric acid*) is secreted by nerve terminals in the spinal cord, cerebellum, basal
ganglia, and many areas of the cortex. It always cause inhibition.

Glutamate
Glutamate is secreted by the presynaptic terminals in many of the sensory pathways entering the central
nervous system, as well as in many areas of the cerebral cortex. It probably always causes excitation.

Serotonin
Serotonin is secreted by nuclei that originate in the median raphe of the brain stem and project to many
brain and spinal cord areas, especially to the dorsal horns of the spinal cord and to the hypothalamus.
Serotonin acts as an inhibitor of pain pathways in the cord, and an inhibitor action in the higher regions of
the nervous system is believed to help control the mood of the person, perhaps even to cause sleep.

Nitric oxide
Nitric oxide is especially secreted by nerve terminals in areas of the brain responsible for

long-term behavior and for memory.Therefore, this transmitter system might in the future explain some behavior and memory functions that thus far have defied understanding. It is not preformed and stored in vesicles in the presynaptic terminal as are other transmitters. Instead, it is synthesized almost instantly as needed, and it then diffuses out of the presynaptic terminals over a period of seconds rather than being released in vesicular packets. Next, it diffuses into postsynaptic neurons nearby. In the postsynaptic neuron, it usually does not greatly alter the membrane potential but instead changes intracellular metabolic functions that modify neuronal excitability.

Neuropeptides

Neuropeptides often cause much more prolonged actions. Some of these actions include prolonged closure of calcium channels, prolonged changes in the metabolic machinery of cells, prolonged changes in activation or deactivation of specific genes in the cell nucleus, and/or prolonged alterations in numbers of excitatory or inhibitory receptors. Some of these effects last for days, but others perhaps for months or years.

Activity 2: Physiology of Direct Motor Pathway

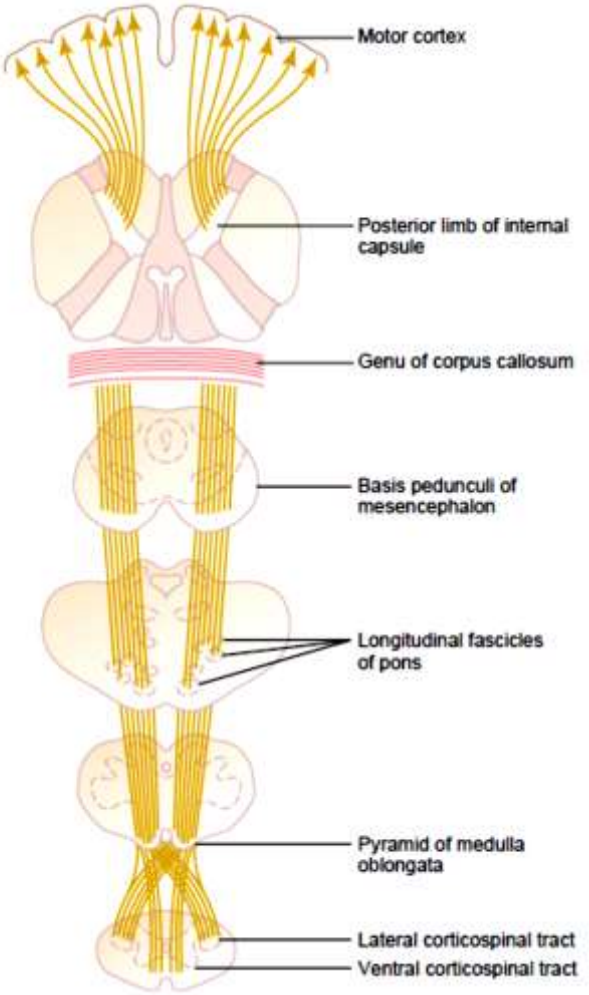
Motor signals are transmitted directly from the cortex to the spinal cord through the *corticospinal tract* and indirectly through multiple accessory pathways that involve the *basal ganglia, cerebellum,* and various *nuclei of the brain stem.* In general, the direct pathways are concerned more with discrete and detailed movements, especially of the distal segments of the limbs, particularly the hands and fingers.

Corticospinal (Pyramidal) Tract

The most important output pathway from the motor cortex is the *corticospinal tract,* also called the *pyramidal tract.* The corticospinal tract originates about 30 per cent from the primary motor cortex, 30 per cent from the premotor and supplementary motor areas, and 40 per cent from the somatosensory areas posterior to the central sulcus. The majority of the pyramidal fibers then cross in the lower medulla to the opposite side and descend into the *lateral corticospinal tracts* of the cord, finally terminating principally on the interneurons in the intermediate regions of the cord gray matter; a few terminate on sensory relay neurons in the dorsal horn, and a very few terminate directly on the anterior motor neurons that cause muscle contraction.

A few of the fibers do not cross to the opposite side in the medulla but pass ipsilaterally down the cord in the *ventral corticospinal tracts.* Many if not most of these fibers eventually cross to the opposite side of the cord either in the neck or in the upper thoracic region. These fibers may be concerned with control of bilateral postural movements by the supplementary motor cortex.

The most impressive fibers in the pyramidal tract are a population of large myelinated fibers with a mean diameter of 16 micrometers. These fibers originate from *giant pyramidal cells,* called *Betz cells,* that are found only in the primary motor cortex. These large fibers represent only 3 per cent of the total. The other 97 per cent are mainly fibers smaller than 4 micrometers in diameter that conduct background tonic signals to the motor areas of the cord.



Activity 3 : Physiology of Indirect Motor Pathway

The term *extrapyramidal (indirect) motor system* is widely used in clinical circles to denote all those portions of the brain and brain stem that contribute to motor control but are not part of the direct corticospinal-pyramidal system.
These include pathways through the basal ganglia, the reticular formation of the brain stem, the vestibular nuclei, and often the red nuclei.

Reticular System

The reticular nuclei are divided into two major groups:
(1) *pontine reticular nuclei*, located slightly posteriorly and laterally in the pons and extending into the mesencephalon
(2) *medullary reticular nuclei*, which extend through the entire medulla, lying ventrally and medially near the midline.

These two sets of nuclei function mainly antagonistically to each other, with the pontine exciting the antigravity muscles and the medullary relaxing these same muscles.

Pontine Reticular System

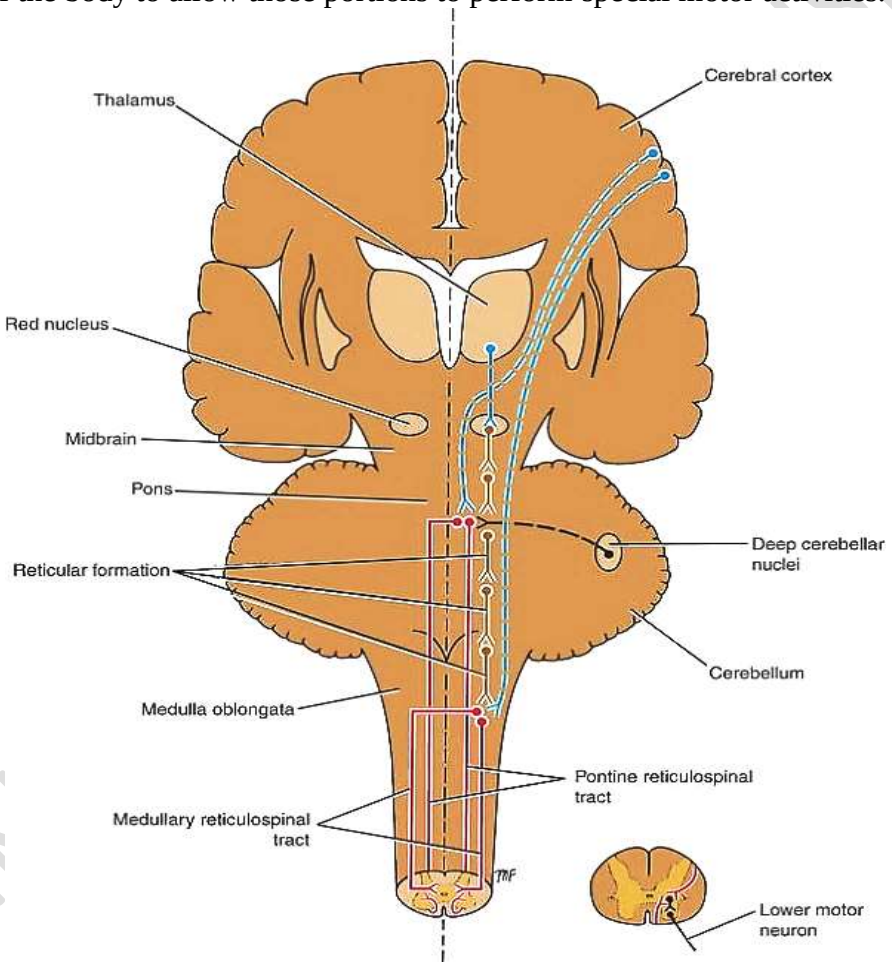
The pontine reticular nuclei transmit excitatory signals downward into the cord through the *pontine reticulospinal tract* in the anterior column of the cord.The fibers of this pathway terminate on the medial anterior motor neurons that excite the axial muscles of the body, which support the body against gravity,the muscles of the vertebral column and the extensor muscles of the limbs. They receive strong excitatory signals from the

vestibular nuclei, as well as from deep nuclei of the cerebellum.

Medullary Reticular System

The medullary reticular nuclei transmit *inhibitory* signals to the same antigravity anterior motor neurons by way of a different tract, the *medullary reticulospinal tract*, located in the lateral column of the cord. The medullary reticular nuclei receive strong input collaterals from (1) the corticospinal tract, (2) the rubrospinal tract, and (3) other motor pathways. These normally activate the medullary reticular inhibitory system to counterbalance the excitatory signals from the pontine reticular system, so that under normal conditions, the body muscles are not abnormally tense.

Yet some signals from higher areas of the brain can "disinhibit" the medullary system when the brain wishes to excite the pontine system to cause standing. At other times, excitation of the medullary reticular system can inhibit antigravity muscles in certain portions of the body to allow those portions to perform special motor activities.

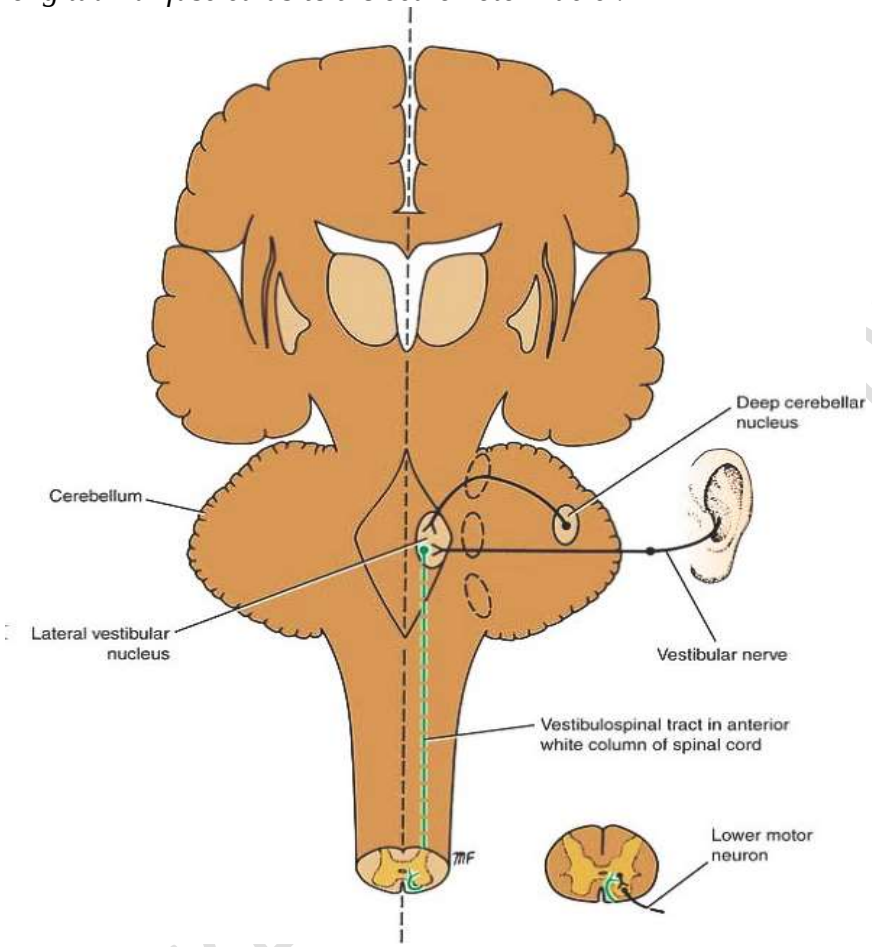


Vestibular System

All the *vestibular nuclei* function in association with the pontine reticular nuclei to control the antigravity muscles. The vestibular nuclei transmit strong excitatory signals to the antigravity muscles by way of the *lateral* and *medial vestibulospinal tracts* in the anterior columns of the spinal cord. Without this support of the vestibular nuclei, the pontine reticular system would lose much of its excitation of the axial antigravity muscles.

When a person changes his or her direction of movement rapidly or even leans the head sideways, forward, or backward, it would be impossible to maintain a stable image on the

retinas unless the person had some automatic control mechanism to stabilize the direction of the eyes' gaze. This results from reflexes transmitted through the *vestibular nuclei* and the *medial longitudinal fasciculus* to the *oculomotor nuclei.*



Tectospinal System

The **tectospinal tract** fibers arise in the superior colliculus of the midbrain and decussate in the dorsal tegmental decussation.

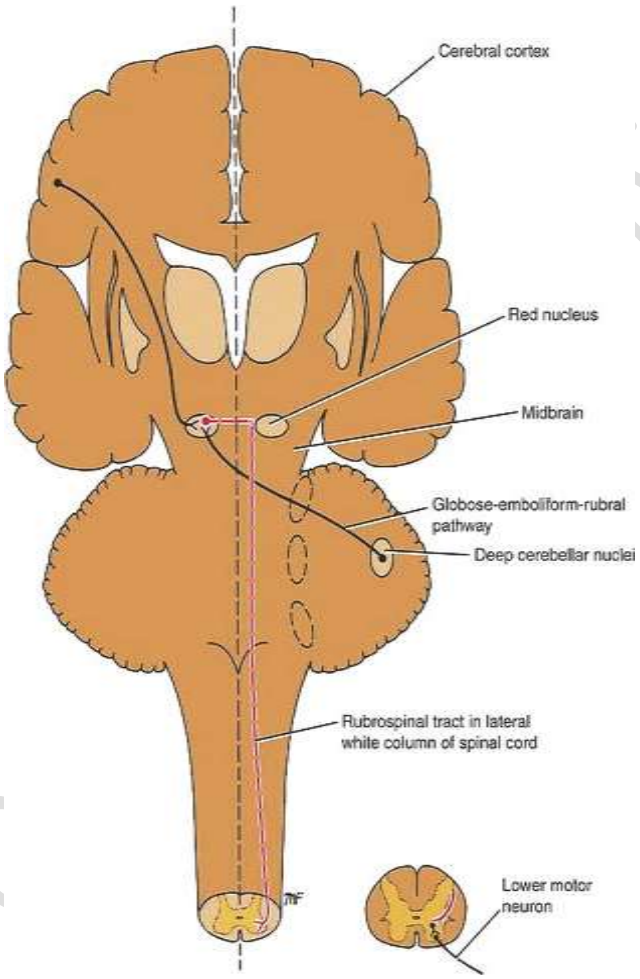
The pathway descends the cord proximal to the ventral median fissure, and most fibers terminate in cervical segments.

The tract is believed to carry motor responses to visual inputs received in the superior colliculus.

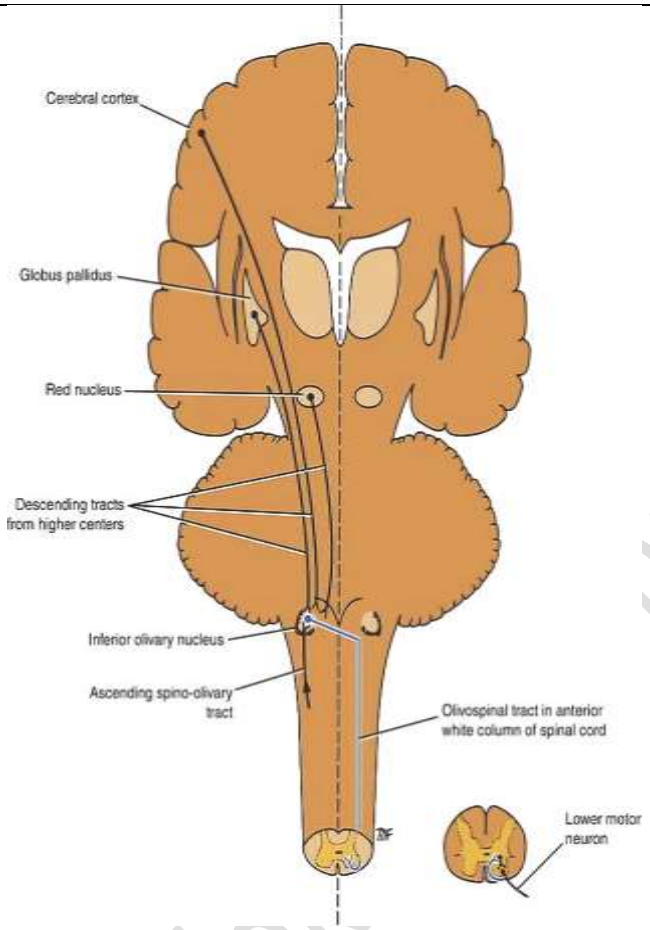
Rubrospinal System

The *red nucleus,* located in the mesencephalon, receives a large number of direct fibers from the primary motor cortex through the *corticorubral tract,* as well as branching fibers from the corticospinal tract as it passes through the mesencephalon. These fibers synapse in the lower portion of the red nucleus, the *magnocellular portion,* which contains large neurons then give rise to the *rubrospinal tract,* which crosses to the opposite side in the lower brain stem and follows a course immediately adjacent and anterior to the corticospinal tract into the lateral columns of the spinal cord. The rubrospinal fibers terminate mostly on the interneurons of the intermediate areas of the cord gray matter, along with the corticospinal fibers, but some of the rubrospinal fibers terminate directly on anterior motor neurons, along with some corticospinal fibers. The red nucleus also has close connections with the cerebellum, similar to the connections between the motor cortex and the cerebellum.

The magnocellular portion of the red nucleus has a somatographic representation of all the muscles of the body, as the motor cortex. However, the fineness of representation of the different muscles is far less developed than in the motor cortex. The corticorubrospinal pathway serves as an accessory route for transmission of relatively discrete signals from the motor cortex to the spinal cord. When the corticospinal fibers are destroyed but the corticorubrospinal pathway is intact, discrete movements can still occur, except that the movements for fine control of the fingers and hands are considerably impaired.
The pathway is excitatory to motoneurons that contract limb flexor muscles.



Olivospinal System
Olivospinal origin: Inferior Olivary nucleus in the medulla oblongata.
This tract descends in the same side of the spinal cord.
It influence the activity of the motor neurons in the anterior gray column



Activity 4 : Physiology of Cerebellum and Basal Ganglia in Motor System

Cerebellum

The cerebellum receives continuously updated information about the desired sequence of muscle contractions from the brain motor control areas.It also receives continuous sensory information from the peripheral parts of the body, giving sequential changes in the status of each part of the body, its position,rate of movement, forces acting on it, and so forth. The cerebellum then *compares*the actual movements as depicted by the peripheral sensory feedback information with the movements intended by the motor system. If the two do not compare favorably, then instantaneous subconscious corrective signals are transmitted back into the motor system to increase or decrease the levels of activation of specific muscles.

The cerebellum also aids the cerebral cortex in planning the next sequential movement a fraction of a second in advance while the current movement is still being executed, thus helping the person to progress smoothly from one movement to the next. Also, it learns by its mistakes, that is, if a movement does not occur exactly as intended, the cerebellar circuit learns to make a stronger or weaker movement the next time. To do this, *changes occur in the excitability of appropriate cerebellar neurons, thus bringing subsequent muscle contractions into better correspondence with the intended movements*.

The intermediate zone of each cerebellar hemisphere receives two types of information when a movement is performed:

(1) information from the cerebral motor cortex and from the midbrain red nucleus, telling the cerebellum the *intended sequential plan of movement* for the next few fractions of a second

(2) feedback information from the peripheral parts of the body, especially from the

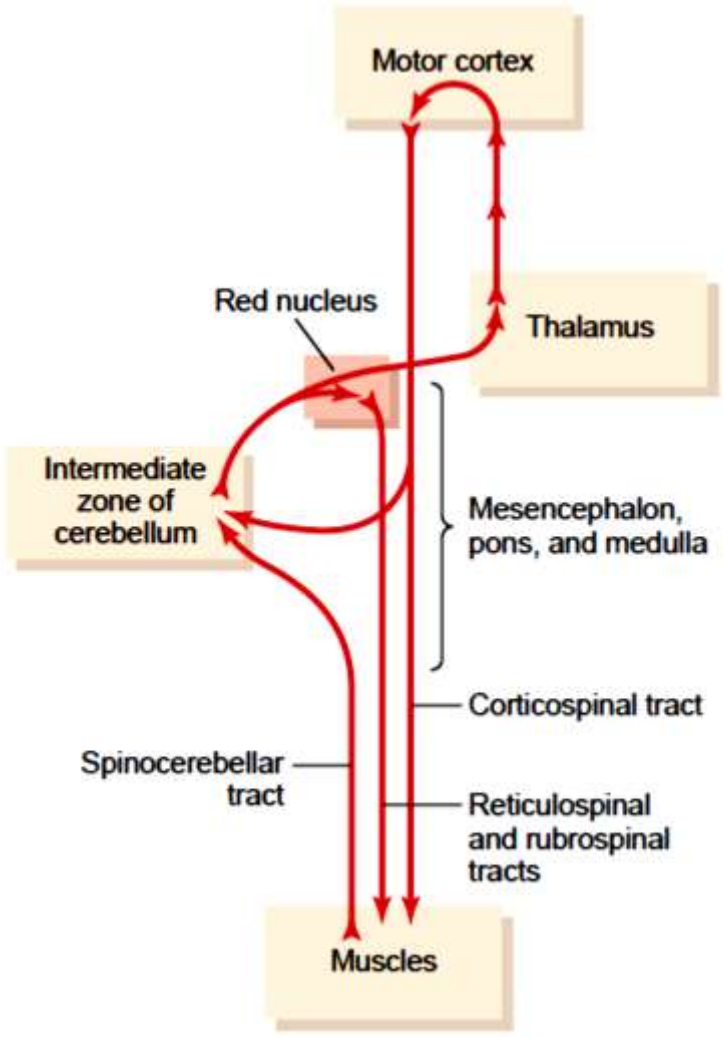
distal proprioceptors of the limbs, telling the cerebellum what *actual movements* result.

After the intermediate zone of the cerebellum has compared the intended movements with the actual movements, the deep nuclear cells of the interposed nucleus send *corrective* output signals

(1) back to the *cerebral motor cortex* through relay nuclei in the *thalamus*

(2) to the *magnocellular portion* (the lower portion) *of the red nucleus* that gives rise to the *rubrospinal tract.*

The rubrospinal tract in turn joins the corticospinal tract in innervating the lateral most motor neurons in the anterior horns of the spinal cord gray matter, the neurons that control the distal parts of the limbs, particularly the hands and fingers. This part of the cerebellar motor control system provides smooth, coordinate movements of the agonist and antagonist muscles of the distal limbs for performing acute purposeful patterned movements.



Basal Ganglia

The basal ganglia, like the cerebellum, constitute another *accessory motor system* that functions usually not by itself but in close association with the cerebral cortex and corticospinal motor control system. The basal ganglia receive most of their input signals from the cerebral cortex itself and also return almost all their output signals back to the

cortex.

On each side of the brain, these ganglia consist of the *caudate nucleus*, *putamen*, *globus pallidus*, *substantia nigra*, and *subthalamic nucleus*. They are located mainly lateral to and surrounding the thalamus, occupying a large portion of the interior regions of both cerebral hemispheres.

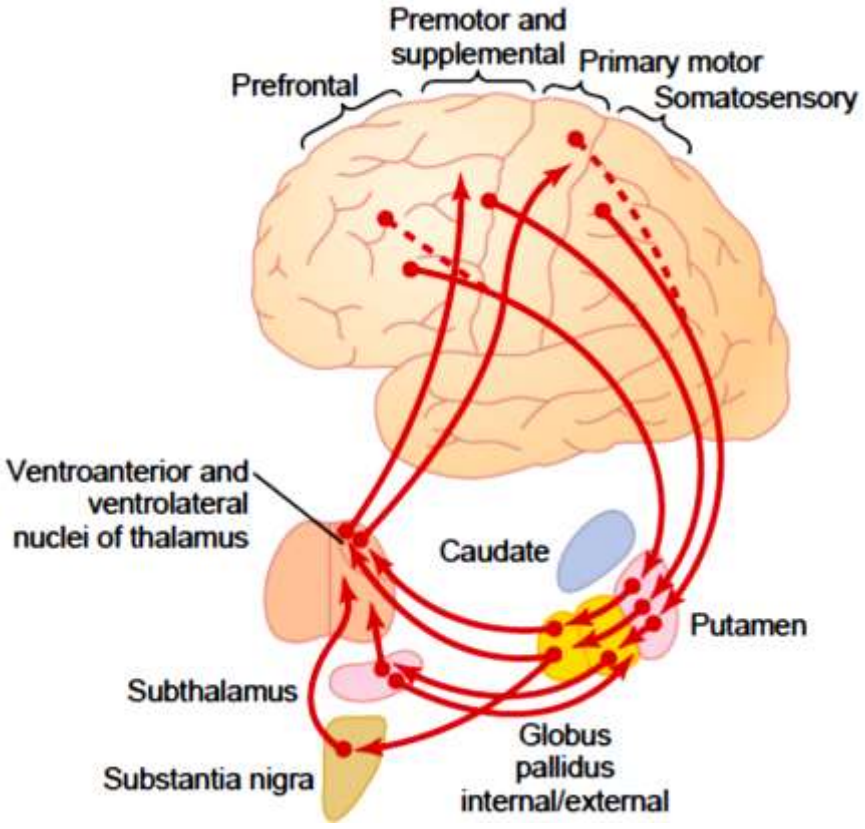
Almost all motor and sensory nerve fibers connecting the cerebral cortex and spinal cord pass through the space that lies between the major masses of the basal ganglia, the *caudate nucleus* and the *putamen*. This space is called the *internal capsule* of the brain.

Neural Pathways of the Putamen Circuit

One of the principal roles of the basal ganglia in motor control is to function in association with the corticospinal system to control *complex patterns of motor activity*.

Putamen circuit begin mainly in the premotor and supplementary areas of the motor cortex and in the somatosensory areas of the sensory cortex. Next they pass to the putamen (mainly bypassing the caudate nucleus), then to the internal portion of the globus pallidus, next to the ventroanterior and ventrolateral relay nuclei of the thalamus, and finally return to the cerebral primary motor cortex and to portions of the premotor and supplementary cerebral areas closely associated with the primary motor cortex.

Functioning in close association with this primary putamen circuit are ancillary circuits that pass from the putamen through the external globus pallidus, the subthalamus, and the substantia nigra, finally returning to the motor cortex by way of the thalamus.

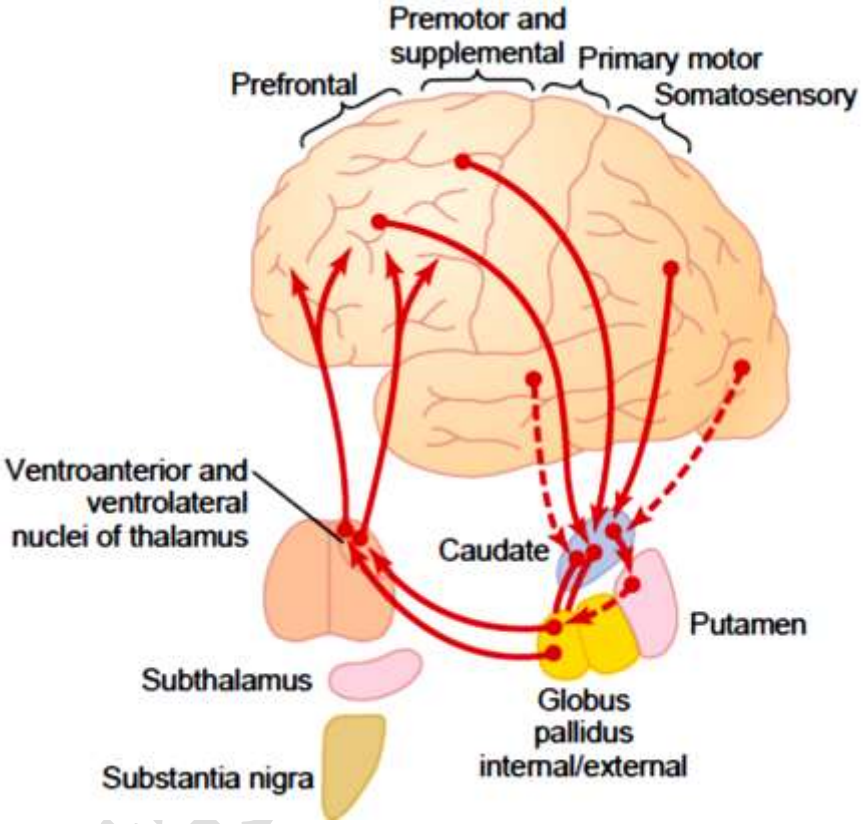


Caudate Circuit

Most of our motor actions occur as a consequence of thoughts generated in the mind, a process called *cognitive control of motor activity*. The caudate nucleus plays a major role in this cognitive control of motor activity.

The caudate nucleus extends into all lobes of the cerebrum, beginning anteriorly in the

frontal lobes, then passing posteriorly through the parietal and occipital lobes, and finally curving forward again like the letter "C" into the temporal lobes. Furthermore, the caudate nucleus receives large amounts of its input from the *association areas* of the cerebral cortex overlying the caudate nucleus, mainly areas that also integrate the different types of sensory and motor information into usable thought patterns.
After the signals pass from the cerebral cortex to the caudate nucleus, they are next transmitted to the internal globus pallidus, then to the relay nuclei of the ventroanterior and ventrolateral thalamus, and finally back to the prefrontal, premotor, and supplementary motor areas of the cerebral cortex, but with almost none of the returning signals passing directly to the primary motor cortex.



Neurotransmitter Substances in the Basal Ganglial System

(1) *dopamine* pathways from the substantia nigra to the caudate nucleus and putamen
(2) *gamma-aminobutyric acid (GABA)* pathways from the caudate nucleus and putamen to the globus pallidus and substantia nigra,
(3) *acetylcholine* pathways from the cortex to the caudate nucleus and putamen, and (4) multiple general pathways from the brain stem that secrete *norepinephrine*, *serotonin*, *encephalin*
(4) *glutamate pathways* that provide most of the excitatory signals that balance out the large numbers of inhibitory signals transmitted especially by the dopamine, GABA, and serotonin inhibitory transmitters.

H **HOMEWORK**

To be collected to your tutor at the day of lab activity

1. Explain about mechanism of neurotransmitter release and mechanism action of excitatory and inhibitory neurotransmitters

	2. Explain about corticospinal tract and its function 3. Explain about extrapyramidal tract and its functions 4. Explain about cerebellum role in motoric pathway 5. Explain about basal ganglia circuits, neurotransmitters and their functions
I	**REFERENCE**
	1. Guyton AC, Hall J, Textbook of Medical Physiology, 11th Edition 2. Greenstein B, Color Atlas of Neurosciences, Neuroanatomy and Neurophysiology 3. Snell RS, Clinically Neuroanatomy, 6th Edition