كلية الطب البشري
Faculty of Medicine

CNS Module-2021

Physiology Lectures Handout

(Lecture 1-14)

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SYNAPTIC TRANSMISSION AND PROCESSING OF SIGNALS IN THE CNS

The synapses are the sites of junction between neurons. The axon of the *presynaptic neuron* divides into about 2000 branches on the average, each of which ends by a knob called the ***synaptic knob.*** A large number of these knobs terminate on the ***dendrites, soma and axon of the postsynaptic neuron*** (e.g. about 10000 knobs terminate on each spinal motor neuron), and at the sites of contact, the knobs are separated from the postsynaptic membranes by gaps filled with ECF called the ***synaptic clefts*** (figure 21).

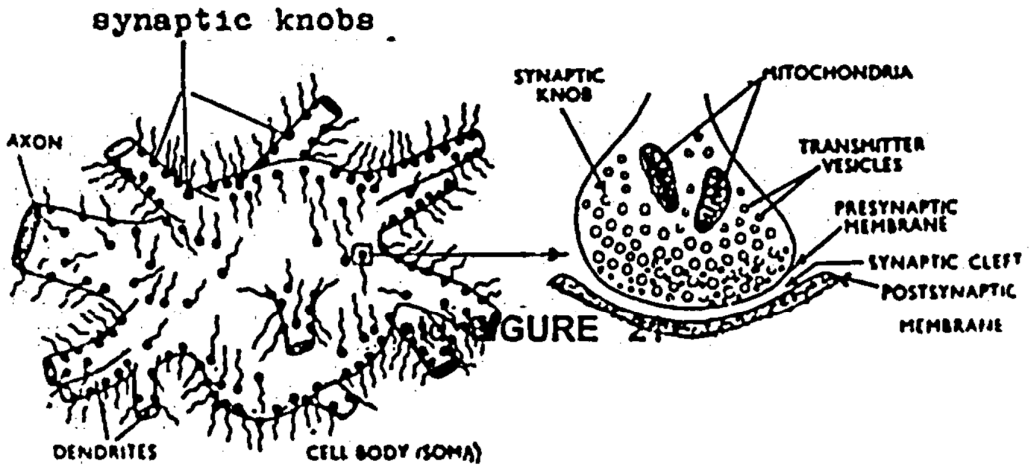


Figure 21 : A spinal motor neuron (AHC) and a synaptic knob on the right.

TYPES OF SYNAPSES

(1) Chemical synapses : These are the ***majority*** in the CNS. The synaptic knobs contain ***vesicles in which neurotransmitters are synthesized,*** and are rich in ***mitochondria*** that provide the required energy. Stimulation of the presynaptic neurons leads to release of the neurotransmitters from these knobs which affect the excitability of the postsynaptic neurons (see below).

(2) Electrotonic (or gap junction) synapses : These are ***few*** but more rapid. The membranes of the pre and post-synaptic neurons come close to each other and ***gap junctions form between them.*** Such junctions constitute ***low-resistance bridges*** through which ions can pass easily, allowing transmission of the depolarization waves directly from one neuron to the other.

(3) Conjoint synapses : These are ***rare*** in the nervous system, and the transmission of signals across them occurs ***both chemically and electrically.***

Mechanism of impulse transmission in chemical synapses

(1) Release of transmitters : Depolarization of the knobs leads to opening of voltage-gated Ca^{2+} channels, which allows ***Ca^{2+} influx*** into the knobs. ***Ca^{2+} causes fusion of the vesicles with the knob's membrane*** at specific ***active zones***, which then rupture leading to release of the transmitter by ***exocytosis*** into the synaptic clefts. The process of fusion involves interaction between 2 proteins, one in the vesicle membrane (= ***synaptobrevin***) and the other in the knob's membrane (= ***syntaxin***). Recently, it was also found that certain proteins called **neurexins** bind the membranes of the presynaptic and postsynaptic neurons together.

(2) Action of transmitters : The transmitter binds to specific receptors in the postsynaptic membrane. This triggers either opening or closure of specific ***ligand gated ion channels*** in that membrane, resulting in electric changes called ***postsynaptic potentials*** (= ***PSPs***) which lead to either excitation or inhibition of the postsynaptic neuron, depending on the nature of the released transmitter (see below).

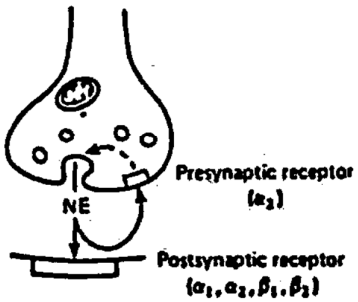


Figure 22 : Presynaptic and postsynaptic receptors at a noradrenergic nerve ending (NE = noradrenaline).

TYPES OF SYNAPTIC RECEPTORS

(1) Presynaptic receptors : These often ***inhibit the release of the neurotransmitters*** e.g. there are ***alpha $_2$ presynaptic receptors*** at the noradrenergic synaptic knobs that are excited by the released transmitter itself but they inhibit its further release (figure 22).

(2) Postsynaptic receptors : There are usually several postsynaptic receptors for each neurotransmitter e.g. :

1. Acetylcholine has 2 types of receptors : Nicotinic and Muscarinic (the latter are 5 types termed M_1 to M_5 receptors).
2. Noradrenaline has 2 types of alpha receptors (1 and 2, each of which has 3 types) and 3 types of beta receptors (1, 2 and 3).
3. Dopamine has 5 types of receptors (called D_1 to D_5 receptors).

TYPES OF POSTSYNAPTIC POTENTIALS

(A) Excitatory postsynaptic potential (EPSP)

This is a state of *transient partial depolarization in the postsynaptic membrane during which the excitability of the postsynaptic neuron to other stimuli is increased.* It occurs in excitatory synapses (at which the transmitter is excitatory e.g. acetylcholine), and is due mainly to an ***increase in*** Na^+ ***or*** Ca^{+2} ***influx*** secondary to opening of their channels.

(B) Inhibitory postsynaptic potential (IPSP)

This is a state of *transient hyperpolarization in the postsynaptic membrane during which the excitability of the postsynaptic neuron to other stimuli is decreased.* It occurs in inhbitory synapses at which the transmitter is **glycine** (see below), and is due mainly to an ***increase in*** Cl^- ***influx***. However, some IPSPs are produced by ***opening of*** K^+ ***channels*** (which increases K^+ efflux) while others can be produced by *closure of* Na^+ *or* Ca^{+2} *channels.*

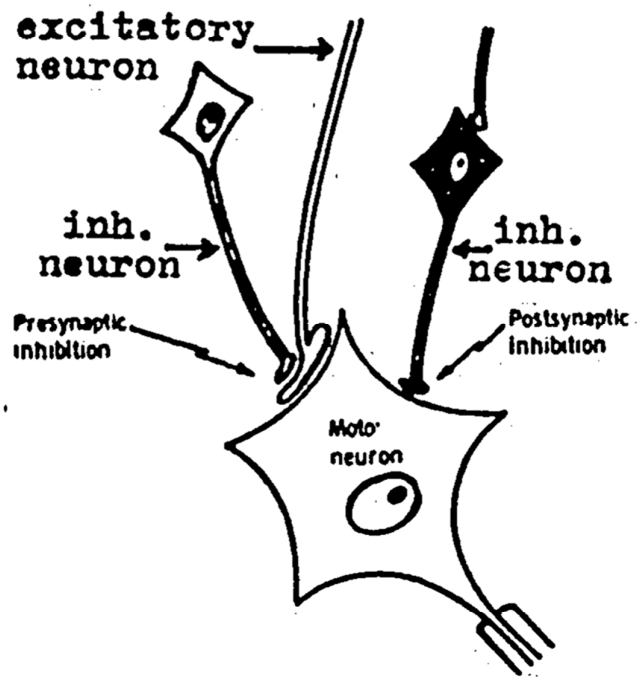


Figure 23 : Types (mechanisms) of synaptic inhibition.

TYPES (MECHANISMS) OF SYNAPTIC INHIBITION

(1) Postsynaptic inhibition

This is the ***commonest mechanism of inhibition*** in the CNS. The terminal knobs of the inhibitory neurons are in direct contact with the postsynaptic neuron (figure 23). Their neurotransmitter is **glycine,** which induces **IPSP** ***by increasing Cl⁻ influx*** (see above).

(2) Presynaptic inhibition

In this type of inhibition, the terminal knobs of the inhibitory neurons ***terminate on the excitatory nerve endings*** (= axo-axonal synapses) *and not on the postsynaptic neurons* (figure 23). It occurs ***in the dorsal horns*** where **enkephalinergic neurons** block pain transmission (refer to the ***analgesia system***, page 35) as well as in other parts in the nervous system in which the transmitter is **GABA.** These inhibitory transmitters decrease the release of the transmitter from the excitatory nerve terminals ***by either a direct effect or by decreasing Ca^{2+} influx*** (thus decreasing post-neuronal excitation).

** *GABA produces the latter effect by decreasing the size of the action potential in the excitatory endings* (which decresaes opening of the Ca^{2+} channels and Ca^{2+} influx). *At the $GABA_A$ & $_C$ receptors, this occurs by increasing Cl- influx while at the $GABA_B$ receptores, it occurs by increasing K^+ efflux*

SUMMATION OF POSTSYNAPTIC POTENTIALS (PSPs)

The PSP (whether excitatory or inhibitory) produced by activity in a single synaptic knob is normally very small and ineffective. However, it is ***not an all or none response*** and can be summated by 2 ways :

(1) Spatial summation : This is more common in the CNS, and is the summation of the PSPs produced by *activation of many synaptic knobs* **at the same time** (commonly *as a result of simultaneous excitation of multiple presynaptic neurons*).

(2) Temporal summation : This is the summation of the PSPs produced by *repeated activation of one synaptic knob* (by continuous stimulation of a single presynaptic neuron). In this case, a new PSP must develop before the previous PSP decays (therefore, the time between successive stimuli must be *less than 15 milliseconds*, which is the time after which a single PSP decays)

** Both types of summation may coexist (= ***temporo-spatial summation***) if several presynaptic neurons are successively stimulated rapidly one after the other at intervals not exceeding 15 milliseconds.

THE CENTRAL EXCITATORY & CENTRAL INHIBITORY STATES

Thousands of excitatory and inhibitory synaptic knobs normally converge on postsynaptic neurons. Therefore, both EPSPs and IPSPs commonly occur simultaneously, and the ***result depends on the algebraic sum of the*** produced ***depolarizing and hyperpolarizing effects.*** Predominance of the former produces a central excitatory state (CES) while predominance of the latter produces a central inhibitory state (CIS).

The central excitatory state favours firing of action potentials from the postsynaptic neurons. The portion in these neurons with the lowest threshold for production of action potentials is the ***initial segment of the axon*** (at and just beyond the axon hillock). For this reason, ***the most rapid transmission of signals normally occurs at the axo-axonic synapses.***

THE PROPERTIES OF SYNAPTIC TRANSMISSION

(1) One way conduction (forward direction) : In synapses, impulses are conducted ***only from the presynaptic to the postsynaptic neurons*** (because the chemical transmitters are present only in the presynaptic knobs).

(2) Delayed conduction (synaptic delay) : There is a delay of impulse transmission in synapses of about ***0.5 millisecond*** due to the time required for release of the neurotransmitter, its diffusion through the synaptic cleft and its binding to and activation of the postsynaptic receptors.

** The **number of synapses in a reflex can be calculated as follows :** The ***total reflex time*** and the time of conduction in the ***afferent and efferent nerves*** are determined. The difference between both represents the time of conduction in the CNS, and is known as the ***central delay***. The number of synapses in the reflex = **Central delay / Synaptic delay** (e.g. if the central delay is 3 milliseconds, the number of synapses = 3 / 0.5 = 6 synapses).

(3) Synaptic fatigue : This is slowing or failure of impulse conduction across synapses that occurs after repetitive stimulation of presynaptic neurons. It may be due to depression of the postsynaptic neurons but it is believed to be primarily due to ***depletion of the neurotransmitter.***

(4) Synaptic afterdischarge : This is continuation of discharge from the postsynaptic neurons for some time ***after stopping stimulation of presynaptic neurons.*** It is due to *persistence of the central excitatory state* produced by the initial stimulus, and it leads to prolongation of discharge of signals from motor neuronal pools (page 48).

(5) Summation of postsynaptic potentials : This occurs by both spatial and temporal mechanisms (page 40).

(6) High sensitivity to the following :

1- Blood pH : Alkalosis increases while acidosis decreases synaptic transmission. Thus, a rise of blood pH from 7.4 to 7.8 leads to convulsions while its fall is associated with drowsiness (or coma in severe acidosis).

2- Blood O_2 level : Hypoxia decreases synaptic transmission, so unconsciousness occurs if the cerebral circulation stops for only 3-5 seconds.

3- Drugs and chemicals :

A- ***Drugs that increase synaptic transmission*** **:**

- Theophylline, caffeine and theobromine.
- Strychnine and tetanus toxin (by blocking the action of glycine).
- Picrotoxin (by blocking the action of GABA).

B- ***Drugs that decrease synaptic transmission :***

- Anesthetic drugs.
- Anti-anxiety and tranquilizer drugs (e.g. diazepam), hypnotic drugs (e.g. barbiturates) and alcohol. All these act by facilitating the action of GABA.

(7) Plasticity and learning :

This means changes in the strength of synaptic transmission (which represent forms of ***learning & memory***, page 129). Such changes are ***presynaptic and postsynaptic***, and they include **potentiation, depression & sensitization**

Divergence of signals in neuronal pools

This is the spread of signals from one input neuron to many output neurons, and it is 2 types :

(1) Divergence in the same tract : This is characteristic of *the cortico-spinal* (= *pyramidal*) *tract*, in which a single cerebral cortical cell can excite about 1000 muscle fibres (figure 26 A).

(2) Divergence into multiple tracts : This is spread of the input signal in 2 separate directions (figure 26 B) e.g. in the dorsal column of spinal cord, the input signals diverge into the spinocerebellar and gracile and cuneate tracts.

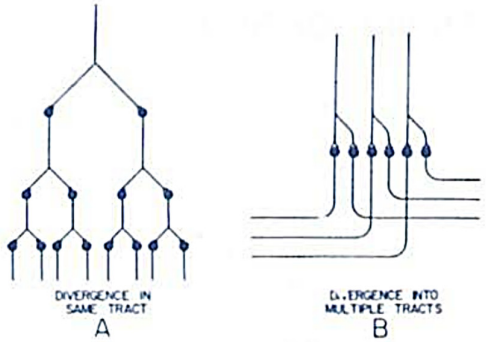


Figure 26 : Divergence in the same tract (A) and in multiple tracts (B).

Convergence of signals in neuronal pools

This is the collection of signals from multiple input neurons to a single output neuron, and it is 2 types :

(1) Convergence from a single source (figure 27 A).

(2) Convergence from multiple sources (figure 27 B).

Both types lead to **summation of impulses**, which is essential for excitation of postsynaptic neurons (page 40).

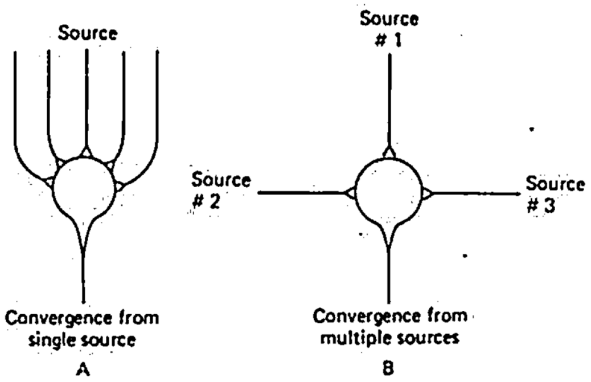


Figure 27 : Convergence from a single source (A) and multiple sources (B).

Prolongation of signals in neuronal pools

Excitatory input signals can lead to a prolonged output discharge even after they stop. This is called **afterdischarge** and it can occur by 2 ways :

(1) Synaptic after-discharge (page 41).

(2) Interneuronal barrages (circuits) : These are 2 types :

(a) Parallel (= multiple or open-chain) circuits : The input signal reaches the output neuron in the form of successive impulses via a number of interneurons that run in parallel (figure 28), resulting in a continued discharge from the output neuron for several milliseconds after the input signal stops.

(b) Reverberatory (= oscillatory or closed-chain) circuits : In this type, the output neuron is repeatedly stimulated through closed circuits of interneurons called ***reverberators*** by a ***positive feedback mechanism*** as follows **:** Collaterals from the interneurons feedback by way of the reverberators to re-excite the output neuron again and again after the input signal stops (most right in figure 28), and this continues for variable periods, after which it stops due to either fatigue of the synaptic transmission or by the effect of an inhibitory input (see below).

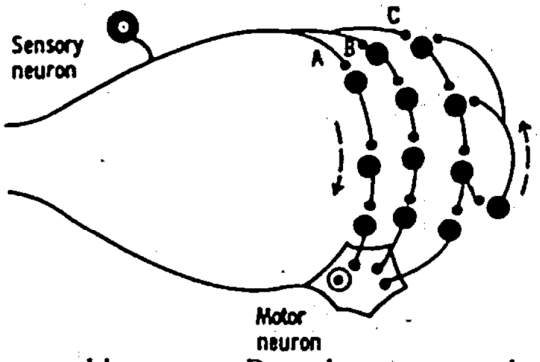


Figure 28 : Interneuronal barrages. Reverberators are shown most right.

Shortening of signals in neuronal pools

An undesired prolonged discharge from a neuronal pool can be prevented by **negative feedback inhibition :** A collateral from an excitatory neuron stimulates an inhibitory interneuron which turns back and inhibits the same excitatory neuron. This function is specially performed by the **Renshaw cells** (figure 29).These cells are *inhibitory interneurons in the anterior horns of the spinal cord gray matter*. The axon of the alpha spinal motor neuron in the anterior horn gives an excitatory ***cholinergic recurrent collateral*** that

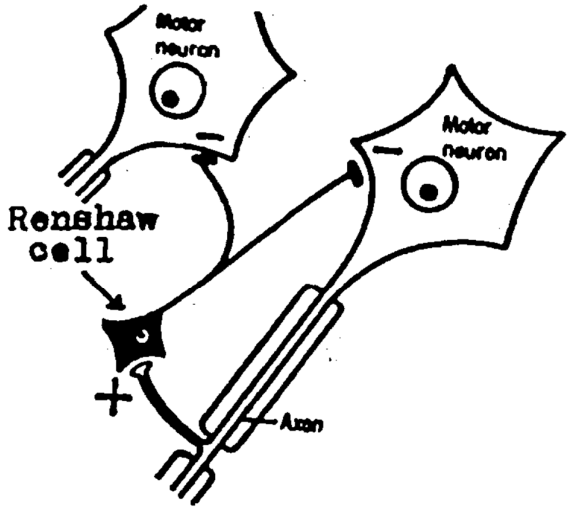


Figure 29 : Negative feedback inhibition by the Renshaw cells.

stimulates a Renshaw cell, and this cell in turn sends signals that inhibit the following neurons through releasing **glycine :**

(a) The original motor neuron, leading to its inhibition (that is commonly called ***negative feedback, collateral, recurrent or Renshaw inhibition***) which results in shortening of the output signals.

(b) The motor neurons in the surrounding area, leading to ***lateral inhibition*** of these neurons, which sharpens the output signals (see next).

** Another mechanism for shortening of signals is present in the cerebellum and is called **negative feed-forward inhibition** (page 108).

Sharpening of signals in neuronal pools

This helps to focus the activity of the output neurons, and it occurs through ***inhibiting the activity of neurons*** in the surrounding pools by one of the following mechanisms :

(1) Lateral inhibition : A collateral from the active output neuron stimulates an inhibitory interneuron which prevents activity in the surrounding neurons. This commonly occurs by the ***Renshaw cells*** (figure 29) as well as in the ***cerebellum*** (page 107) and the retina of the eye by the ***horizontal cells*** (refer to special senses)

(2) Reciprocal inhibition circuits : Such circuits characteristically coordinate many spinal reflexes. For example during the stretch reflex, the input fibres directly excite the motor neurons of the stretched muscle and simultaneously stimulate an interneuron that inhibits the surrounding neurons particularly those supplying the antagonist muscle (figure 30) resulting in sharpening of signals to the stretched muscle as well as its smooth contraction.

The same occurs during the withdrawal reflex (figure 33). The spinal inhibitory interneurons are short plump neurons with thick axons. They are called ***Golgi bottle neurons,*** and they produce direct postsynaptic inhibition.

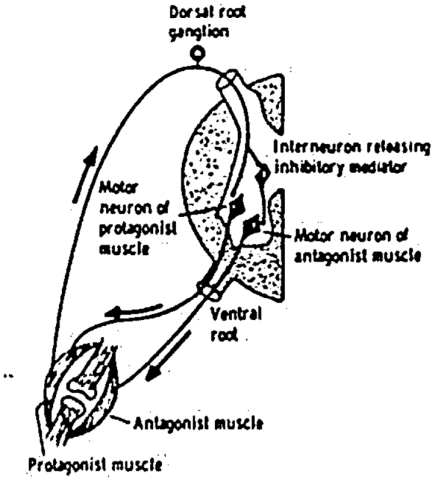


Figure 30 : A reciprocal inhibition circuit acting during the stretch reflex.

THE SENSORY RECEPTORS

The sensory receptors are specialized structures located at the peripheral ends of sensory (= afferent) neurons, and they may be a part of the neuron or a separate organ. They are excitable structures, since they respond to various forms of energy (i.e. various stimuli) by generating action potentials.

FUNCTIONS OF THE SENSORY RECEPTORS

(1) They act as detectors and transducers : They detect energy changes in both the external and internal environments and transform such changes into action potentials (i.e. nerve impulses).

(2) They inform the CNS about changes occurring inside and outside the body : The nerve impulses generated at the receptors are transmitted to the CNS via ***afferent neurons*** where they give rise to various sensations and initiate appropriate reflex actions that ***maintain homeostasis.*** Accordingly, ***the CNS becomes almost useless without receptors..***

PROPERTIES OF THE SENSORY RECEPTORS

(1) SPECIFICITY (differential sensitivity)

Each type of receptors responds to a specific form of energy called its **adequate stimulus** and produces a particular sensation. Some receptors can respond to other stimuli called ***inadequate stimuli*** e.g. the adequate stimulus of the retinal receptors is light, but they can also be stimulated by mechanical pressure. However, to produce a response, the threshold of such inadequate stimuli must be high, and they *produce the same sensation for which the receptor is specialized* (i.e. light in case of retinal receptors).

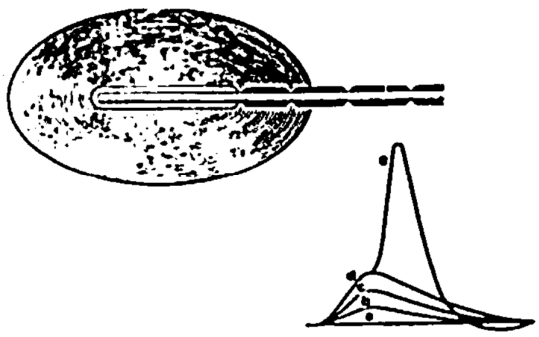


Figure 1 : the Pacinian corpuscle. (a, b, c and d) are generator potentials in response to gradually-increasing pressures, while (e) is an action potential.

(2) EXCITABILITY (THE RECEPTOR POTENTIAL)

This is the property of responding to stimuli by generating action potentials. It has been studied in certain mechanoreceptors called ***Pacinian corpuscles***. Each corpuscle consists of a sensory nerve ending surrounded by multiple concentric lamellae of connective tissue, and the *terminal part of the nerve ending is unmyelinated* while its remaining part is myelinated, and *the first node of Ranvier is present inside the corpuscle* (figure 1).

When the corpuscle is not stimulated, the sensory nerve ending is in the polarized state (with a resting membrane potential about -70 mV). However, if it is stimulated (by applying pressure), the *unmyelinated part* is partially depolarized due **to *increased Na^+ influx secondary to Na^+ channel activation***. This state of partial depolarization of the sensory nerve ending is called the **receptor or generator potential**, and its magnitude is ***proportionate to the intensity of the stimulus*** (a, b, c and d in figure 1).

The receptor potential is ***passively conducted to the first node of Ranvier*** (by local circuits of current flow) causing its depolarization, and if this reaches the firing level, it initiates an action potential (e in figure 1) that is propagated along the afferent nerve to the nervous system.

The ***threshold receptor potential that discharges an action potential is about 10 mV***, and if its magnitude rises above that level (depending on the intensity of the stimulus), the frequency of discharge increases proportionately (figure 2).

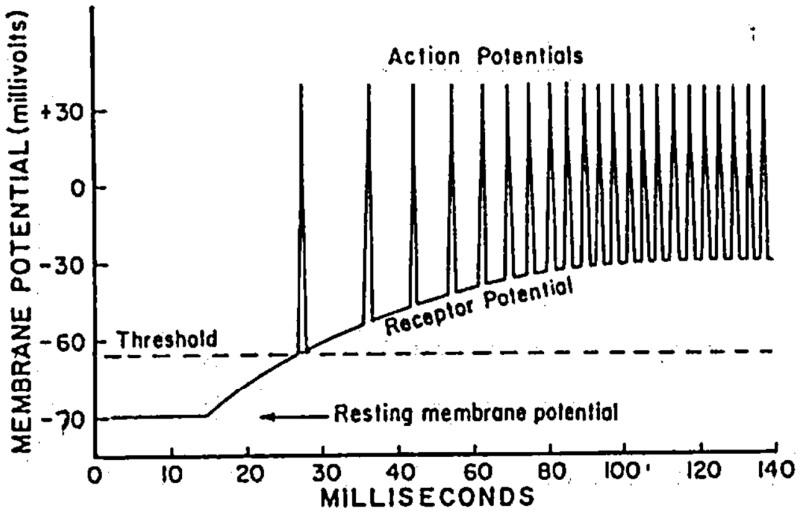


Figure 2 : Relation between the receptor potential (RP) & action potentials (APs). As the (RP) rises above threshold, the frequency of (APs) increases.

Properties (characteristics) of the receptor potential

(1) It *does not obey the all or none law*, so it *can be graded.*
(2) It is *not followed by an absolute refractory period,* and its *duration is long* (about 5 milli-seconds), so it *can be summated*
(3) It *is not blocked by local anesthetic drugs .*
(4) It leads to *a propagated action potential on reaching the threshold level.*

(3) DISCHARGE OF IMPULSES

The frequency of discharge of impulses from receptors depends on the intensity of stimulation, and it determines the magnitude of the perceived sensation. It occurs according to the ***Weber-Fechner law*** which states that " ***the frequency of discharge from receptors is directly proportional to the logarithm of intensity of the applied stimuli*** ". However, this law was found to *apply only to high intensities of stimulation*, and the following power function (known as the ***power law***) expresses the mathematical relation between the intensity of stimulation and the frequency of discharge more accurately :

$$R = KS^{\Lambda}$$

Where **R** is the sensation felt, **S** is the intensity of the stimulus, **K and** Λ are constants (which vary with each type of sensation).

(4) ADAPTATION

This is a decline in the frequency of discharge of action potentials from receptors that occurs on ***maintained stimulation by stimuli that have a constant strength***. **Adaptation is different from fatigue and the following table shows the differences between both :**

Mechanism of adaptation

The following are probable mechanisms for adaptation of receptors :

(1) Accommodation to the stimulus in the terminal nerve fibre that occurs secondary to progressive inactivation (closure) of the Na^{+} channels in the nerve fibre membrane (which decreases the magnitude of the receptor potential and consequently the frequency of discharge).

(2) Readjustment in the structure of the receptor itself after its initial distortion by the stimulus (so that the receptor potential is no longer elicited even though the stimulus is maintained).

CODING OF SENSORY INFORMATION

This is the ability of the nervous system to discriminate (or identity) the ***modality*** **(= *type*)**, ***locality and intensity of various sensations,*** *although all sensations are transmitted from the receptors to the higher centres in the same form* (*i.e. as action potentials*).

(1) MODALITY DISCRIMINATION

The various sensory pathways are discrete (i.e. separate from each other), and the modality of a certain sensation is ***discriminated at the specific brain area where its pathway terminates.*** This agrees with Muller's law.

Muller's law of specific nerve energies

This law states that *stimulation of a certain sensory pathway* ***no matter how or where*** *produces the sensation to which its receptors are specialized*. Such effect is also called the ***labeled line principle*** i.e. each sensory pathway (*from the receptors till the termination at the higher centres*) is labeled for a specific sensation (so stimulation of the retinal receptors whether by light or mechanically by pressure always produces a light sensation, page 1).

(2) LOCALITY DISCRIMINATION

The discrimination of the locality of a certain sensation also depends on the specific pathway of that sensation. When this pathway is stimulated anywhere along its course, the evoked sensation is projected to (i.e. referred to) the location of its receptors. This effect is called **" law of projection "**, and it is evident in patients whose limbs are amputated, who *may feel severe pain in the phantom limb* (*i.e. the non-existing limb*) *due to irritation of the sensory nerves at the site of amputation.*

(3) INTENSITY DISCRIMINATION

The discrimination of the intensity of a certain sensation depends on the number of ***activated receptors and their frequency of discharge*** as well as on the ***state of nerve centres*** (if they are depressed e.g. due to O_2 lack or hypoglycemia, the sensations become dull and their intensity is decreased).

THE SOMATIC SENSATIONS

The various sensations in the body include **(1) Somatic sensations** (from the skin and deep tissues e.g. muscles, joints and bones) **(2) Visceral sensations (3) Special sensations** (vision, hearing, smell, taste and equilibrium) **(4) Organic sensations** (e.g. hunger, thirst and sexual sensations).

The sensory pathway or axis

The perception of a certain sensation requires that its pathway (or axis) should be intact. A sensory axis includes **(1)** *A receptor* **(2)** *An afferent* (*or sensory*) *nerve* that transmits the signals to the nervous system **(3)** *A transmitting tract to the higher centres and cortical sensory areas.*

The sensory unit and the receptive field

The ***sensory unit*** consists of a single afferent nerve and all its peripheral branches whle the ***receptive field*** is the area supplied by a certain unit. There is a ***considerable overlap of the receptive fields*** of neighbouring sensory units. This is evident in the skin in which each spinal nerve innervates a definite area called a ***dermatome*** (figure 5) and these show ***marked overlapping***

Recruitment of receptors and sensory units

Threshold (or minimal) stimuli activate only the highly-sensitive receptors, leading to a little discharge of impulses. However, as the intensity of stiimulation increases, more receptors become activated (= ***recruitment of receptors***) and more sensory units discharge (= ***recruitment of sensory units***) and this is interpreted by the higher centres as ***an increase in the intensity of the sensation.***

CLASSIFICATION OF THE SOMATIC SENSATIONS

The somatic sensations can be **classified in 2 ways :**

(A) ACCORDING TO THE SITE OF THE SENSATION

(1) Superficial (or exteroceptive) sensations : These are the skin sensations (***pain, touch and temperature***).

(2) Deep sensations : These are the sensations from skeletal muscles, tendons, joints, bones and ligaments, and they include the following types : **(a) Proprioceptive sensations :** These include the ***sense of position and the sense of rate of movement*** **(= *kinesthetic sensation*) (b) Pressure sense (c) Muscle tension sense (d) Muscle sense** (= pain elicited by firm squeeze of skeletal muscles). Sometimes the **vibration sense** is included in this group.

(3) Combined or synthetic senses : These include **stereognosis and the vibration sense (and sometimes tactile discrimination).**

(B) ACCORDING TO THE MODALITY OF THE SENSATION

(1) Mechanoreceptive sensations : These include the touch, pressure, vibration, itch and tickle sensations, as well as muscle tension and the proprioceptive sensations.

(2) Thermoreceptive sensations (heat and cold sesations).

(3) Pain sensation.

**** During testing any sensation, the patient's eyes must be closed.**

THE MECHANORECEPTIVE SENSATIONS

(1) TOUCH (TACTILE) SENSATION

There are 2 types of touch (tactile) sensation :

[A] Crude touch : This is a **poorly-localized gross tactile sensation.**

- ***Receptors*** **:** Free nerve endings and hair end organs.
- ***Afferent nerves*** **:** *A-delta nerve fibres.*
- ***Central pathway*** **:** Ventral spinothalamic tract (page 22) and also partly in the gracile and cuneate tracts (page 24).
- ***Testing*** **:** By stroking the skin lightly with *a piece of cotton.*

[B] Fine touch : This includes **tactile localization and discrimination, stereognosis and the sense of texture of material** (see below).

- ***Receptors*** **:** Meissner's corpuscles and Merkel's disks.
- ***Afferent nerves*** **:** *A-beta nerve fibres.*
- ***Central pathway :*** The gracile and cuneate tracts (page 24).

Tactile Localization (topognosis)

This is the ability to localize a touched skin point *while the eyes are closed.* It is ***tested*** by touching the skin lightly ***with a marker pencil*** (e.g. a charcoal pencil) and the subject is asked to touch the stimulated point by another pencil. The closer the 2 touch points to each other, the more accurate is the localization. This sensation is ***affected by the same factors that affect tactile discrimination*** (see next).

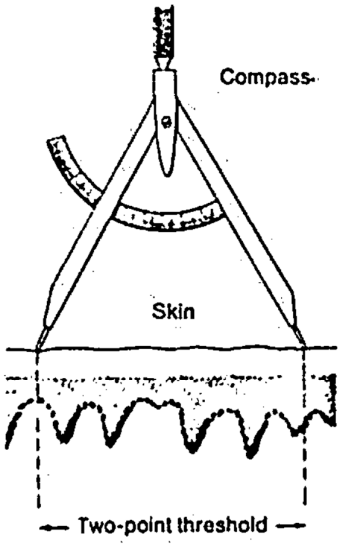


Figure 6 : The Weber compass.

Tactile Discrimination (T.D. or 2 point discrimination)

T.D. is the ability to distinguish 2 touch stimuli applied simultaneously to the skin as 2 separate points of touch. It is ***tested*** by *repeated* touching the skin with the 2 blunt points of a ***Weber compass*** (figure 6), starting by a closed compass, then increasing the distance between its limbs gradually till finding the ***2-point threshold*** (i.e. the minimal distance at which the 2 points are separately perceived). It is a highly educated cortical sensation that requires *excitation of 2 separate receptors and 2 separate areas in the sensory cortex*. Accordingly, it is more acute (i.e. the 2-point threshold is small) in areas that are ***rich in receptors and their representation in the sensory cortex is wide*** such as the lips and fingers (e.g. it is only about 3 mm in the fingers) while it is less acute (i.e. the 2-point threshold is large) in areas lacking these characteristics such as the shoulders, thighs and back (e.g. it is 65 mm or more in the back).

Other cutaneous sensations (e.g. pain and cold) can also be tested for localization and discrimination. However, the discrimination acuity is ***maximal in the fovea centralis*** (the central part of the eye's retina) which can distinguish very close light rays (refer to special senses).

Stereognosis

This is the ability to recognize the nature of objects by handling them ***without using vision*** (from their shapes, sizes, weights, etc.). It is tested by giving the subject ***a familiar object*** (e.g. a key, pen or coin) and ***with closed eyes,*** he is asked to recognize its nature. It is a *highly educated cortical sensation* that depends mainly on the tactile and pressure sensations as well as the *integrity of the high cortical sensory centres.*

The sense of texture of material is *a type of stereognosis*. It is the sensation evoked by touching materials and is concerned with identification of their natures. It is tested by asking the subject to differntiate between various materials e.g. pieces of cloth whether made of silk, wool or cotton.

(2) THE PRESSURE SENSATION

This sensation is perceived mainly by the ***Pacinian corpuscles and Ruffini's endings*** in the skin (for light pressure) and subcutaneous tissues (for deep pressure). It is tested by asking the subject to differentiate between various weights *without lifting them* (by placing them in his hand *while it is supported on a table*). Like touch, there are 2 types of pressure sensation : **fine** (which is transmitted by the gracile and cuneate tracts) and **crude** (which is also transmitted by the ventral spinothalamic tract).

The muscle tension sensation is the sensation evoked by traction on the tendons and is concerned with *discrimination of weights during lifting them*. Its receptors are the Golgi tendon organs, and is transmitted by the gracile and cuneate tracts. It is tested by asking the subject to differentiate between various weights placed in *his unsupported hand*.

(3) THE VIBRATION SENSE

This is the sense of buzzing (or thrill) that is felt when the *base of a vibrating tuning fork* is placed on the skin. During testing, it is better to place the tuning fork ***on a bony prominence*** e.g. the lower end of the radius bone or one of the malleoli, because ***bone magnifies the sense of vibration***. It is produced as a result of ***rhythmic pressure stimuli*** (which is interpreted as vibration) that stimulate ***2 types of rapidly adapting mechanorecepiors*** (a) ***Meissner's corpuscles***, which respond to vibrations up to *80 Hertz* (b) ***Pacinian corpuscles***, which respond to vibrations up to *800 Hertz*.

Vibration is closely related to proprioception. Both are transmitted by the ***gracile and cuneate tracts***, and both are impaired if these tracts degenerate e.g. in cases of pernicious anemia, tabes dorsalis and diabetes mellitus.

(4) THE TICKLE AND ITCH SENSATIONS

Tickle is a pleasurable sensation (often causing laugh) that results from mild tactile stimulation of the skin, while itch is an annoying sensation that results from skin irritation by moving tactile stimuli (e.g. a crawling flea).

- ***Receptors*** : Rapidly-adapting free nerve endings.
- ***Afferent nerves*** : Unmyelinated type C nerve fibres.
- ***Central pathway*** : Ventral spinothalamic tract.

Itch often initiates the ***scratch reflex*** which helps removal of the stimulus, and also ***initiates pain signals*** which help suppression of this sensation.

(5) THE PROPRIOCEPTIVE SENSATIONS

These sensations arise mainly from receptors in the deep structures (specially the muscles & joints) including the *muscle spindles and Golgi tendon organ-like receptors in addition to spray (Ruffini's) endings and Pacinian corpuscles in the synovia and ligaments of joints*. They are transmitted to the high centres by the gracile and cuneate tracts, and include 2 types :

(a) Sense of position (static proprioception)

This is the ***conscious perception of the position of different parts of the***

body with respect to each other. It is tested by placing one of the patient's limbs, toes or fingers in an unusual position (with his *eyes closed*), and asking him to place the corresponding part in the other side at a similar position

(b) Sense of movement (dynamic proprioception)

This is the ***sensation of movement of joints.*** It is tested by moving one of the patient's fingers or toes *passively* (i.e. by the examiner) while *his eyes are closed,* and asking him to determine the start and end of the movement, as well as its rate and direction.

** Both types of proprioception are frequently called **kinesthetic sensations** (although only the dynamic type is kinetic).

THE THERMORECEPTIVE SENSATIONS

THE THERMORECEPTORS

There are 2 types of thermoreceptors **(1) Internal thermoreceptors** located in the anterior hypothalamus for detection of the head temperature **(2) External thermoreceptors :** These include cold and warmth receptors and also certain pain receptors that are stimulated only by extreme degrees of heat and cold (leading to the freezing cold and burning hot sensations). These receptors are located ***under the epithelial layer of the skin***, and there are ***discrete cold and warmth sensitive spots*** (with thermally-insensitive areas in between), and the ***cold spots are 4-10 times more in number.***

THE WARMTH RECEPTORS are special ***free nerve endings*** that transmit warmth sensation along ***type C afferent nerve fibres*** and respond to temperatures from 30 ° C to over 45 °C. 2 receptors called **VR-1 and VRL-1** that respond to high noxious heat have also been described **(VR = Vanilloid Receptor).**

THE COLD RECEPTORS **:** The receptors for moderate cold are the **CMR-1** (= Cold and Menthol-sensitive receptors 1). They are free nerve endings that transmit cold sensation along both ***type C and type A-delta nerve fibres*** They respond to temperatures from 10 °C to 38 °C, and also **briskly** (i.e. for a very short time) at about 45 °C (figure 7).

As a result of the overlap of the temperature ranges that stimulate the various thermoreceptors, the discrimination of temperature depends on the degree of stimulation of each of these receptors. ***At temp. below 10 °C and above 45 °C, the thermosensitive pain receptors are brought into action.***

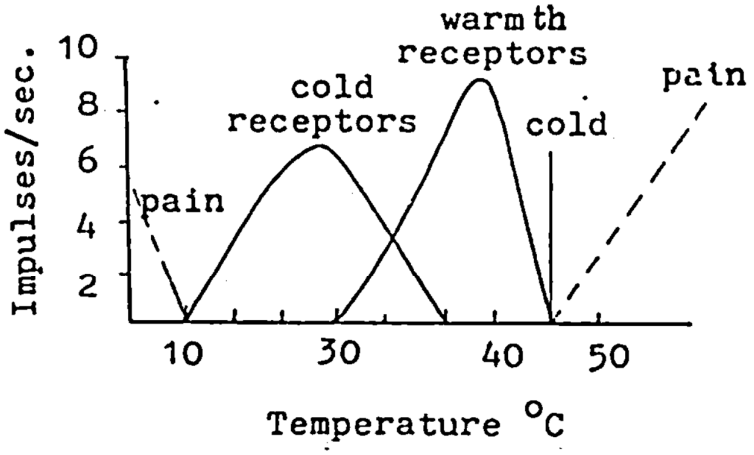


Figure 7 : Frequency of discharge from thermoreceptors at different temp.

Paradoxical cold sensation

When the skin is exposed to a temperature of about 45 °C, ***a sensation of cold is first felt*** then the hot sensation follows. This is called paradoxical cold sensation, and it is due to the ***brisk stimulation of the cold receptors at this temperature and also their greater number than the warmth receptors.***

Stimulation of the thermoreceptors

Thermoreceptors are stimulated ***chemically by changes in their metabolic rates*** that are produced by the thermal stimuli. They detect the ***absolute temperature of the surrounding tissues*** (so the external thermoreceptors detect the subcutaneous tissue temperature). For this reason, cutaneous V.C. produces a cold sensation even in hot weather (e.g. in hemorrhage), while V.D. produces a warmth sensation even in cold weather (e.g. on drinking alcohol).

Adaptation of the cutaneous thermoreceptors

These receptors are ***moderately adapting and the warmth receptors adapt more rapidly than the cold receptors*** (page 7).

Central pathway of thermal sensations

The thermal signals are transmitted from one side of the body to the opposite higher centres with the ***pain signals by the lateral spinothalamic tract***, (page 22) and terminate at the reticular formation and thalamus, and some fibres reach the cortical sensory areas. Recently, it was reported that the thermal sensations also project to the ipsilateral cortex.

PAIN SENSATION

Pain is a specific unpleasant sensation but ***its adequate stimulus is not specific*** (it is produced by any ***noxious stimulus*** whether mechanical, thermal or chemical). It has a ***protective function*** and is almost ***non-adapting***.

Pain receptors (the noci ceptors)

These are ***specific naked free nerve endings***. They are more abundant in the skin than in the deep tissues and viscera, and they are stimulated mainly ***chemically*** by substances released from damaged tissues specially ***K , bradykinin and certain proteolytic enzymes.***

Fast and slow pain

According to its site, pain may be classified into ***cutaneous, deep and visceral pain.*** However, it is more frequently divided into **fast and slow types,** the differences between which are shown in the following table **:**

	FAST PAIN	SLOW PAIN
Site (origin)	Almost only in the Skin	Skin, deep tissues and viscera
Stimulus	Mainly the mechanical and thermal noxious stimuli	Mechanical, thermal and chemical. noxious stimuli
Quality	Pricking (sharp or acute)	Burning (aching or chronic)
Perception	0.1 second after stimulation	1 second or more after stimulation
Duration	Less than one second	Many seconds to a few minutes
Localization	Well-localized	Diffuse (poorly-localized)
Afferent nerve	Type A-delta nerve fibres which release glutamate	Type C nerve fibres which release substance P
Carrying tract	Neospinothalamic tract	Paleospinothalamic tract
Centre in CNS	Cerebral cortex	Reticular formatiom & thalamus
Initiated reflexes	Somatic protective reflexes	Autonomic and somatic reflexes
Summation	Does not occur	Marked (becoming intolerable)
Depression	By pressure and hypoxia	By local anesthetic drugs

Central perception of pain sensation

Pain sensation is transmitted to the higher centres by the **lateral spino-thalamic tract** (page 22) which consists of 2 parts **(1)** ***Paleospinothalamic tract*** **:** This transmits slow pain and terminates *subcortically* specially at the reticular formation and the intralaminar thalamic nuclei **(2)** ***Neospinothalamic tract*** **:** This transmits fast pain and its fibres relay first in the ventrobasal complex of the thalamus (specially the ventral postero-lateral nucleus) then finally terminate at the cortical somatic sensory areas (figure 8)

** Removal of the cortical somatic sensory areas does not abolish perception of both types of pain. This indicates that pain is generally perceived mainly ***at a subcortical level*** (in the thalamus, reticular formation and other lower centres). However, *the cortical centres are essential for interpretation of the quality and locality of fast pain.*

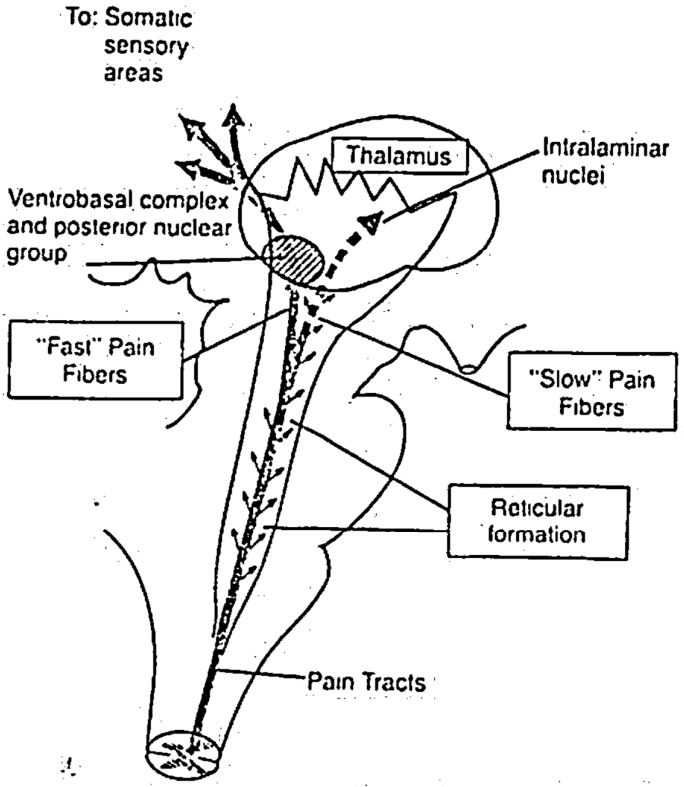


Figure 8 : Central termination of the fast pain and slow pain nerve fibres.

CUTANEOUS PAIN

This may be fast well-localized pricking pain or slow diffuse burning pain ***It*** **is** ***not referred***, and is *tested* by either pricking the skin with a pin or by heating the subject's skin and recording the temperature at which pain occurs (the normal pain threshold is 45 °C). It is associated with **(1)** *Somatic effects*

(the withdrawal reflex) **(2)** *Autonomic effects* (usually symp.e.g V.C., tachycardia & rise of the arterial blood pressure, but parasymp. effects may occur if pain is severe e.g. V.D., bradycardia & hypotension) **(3)** *Hyperalgesia.*

CUTANEOUS HYPERALGESIA

This is pathological hypersensitivity to pain and it is 2 types :

(1) Primary hyperalgesia : This occurs in the ***injured skin area*** and the surrounding area of flare (= V.D.), in which the ***pain threshold is lowered,*** so that *non-noxious stimuli become painful* (= ***allodynia***). It is due to sensitization of the pain receptors by some substances released from the damaged tissues (histamine, kinins, K^+, certain enzymes or prostaglandins). It has also been suggested to be due to release of ***substance P*** from nerve endings as a result of a ***local axon reflex*** through ***antidromic impulses,*** which sensitizes the pain nerve endings and also produces V.D. (i.e. flare) of the triple response (refer to circulation).

(2) Secondary hyperalgesia : This occurs in the ***healthy skin area*** beyond that of primary hyperalgesia (figure 9). In this area, the ***pain threshold is not lowered but it is normal or even elevated.*** However, the pain aroused from such area is ***prolonged and exaggerated.*** This is explained by the **convergence facilitation mechanism** which occurs as follows: The central neurons are facilitated by impulses discharged from the area of injury, and afferent fibres from the area of secondary hyperalgesia converge on the facilitated neurons, thus the pain aroused at this area becomes exaggerated.

** Secondary hyperalgesia can occur ***in absence of primary hyperalgesia*** if there is *central facilitation of sensory transmission.* This occurs in certain thalamic and spinal cord lesions, and also in some cases of visceral pain (in which the facilitatory impulses are discharged from the diseased viscus).

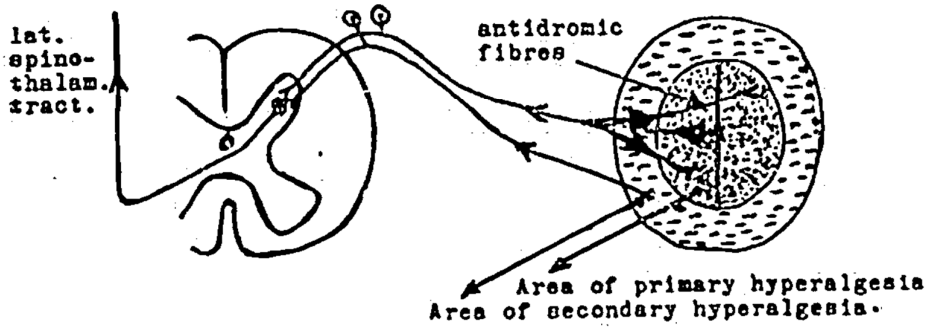


Figure 9 : Areas of primary and secondary cutaneous hyperalgesia.

REFERRED (RADIATING) PAIN

This is pain that is felt away from its original site. It is most common with ***visceral pain*** (deep pain may be referred but *cutaneous pain is not referred*). The structure in which pain originates and the structure to which pain is referred ***develop from the same embryonic segment,*** and frequently they are ***far away from each other*** due to ***migration of the various organs during devlopment.***

EXAMPLES OF REFERRED PAIN

(1) Pain of an inflamed gall bladder is transmitted by afferent *phrenic nerve fibres* (due to *irritation of the diaphragm*) to the 3rd, 4th and 5th cervical spinal segments, so it is usually referred to the ***tip of the right shoulder.***

(2) ***Cardiac pain*** is usually referred to the ***left shoulder and inner side of the left arm*** (less frequently to the right shoulder or the epigasrium).

(3) Pain from ***the kidneys and ureters*** is referred to the ***testicular region.***

(4) ***Gastric pain*** is referred to the abdominal surface above the umbilicus.

(5) Pain of ***appendicitis is referred to the umbilical region.***

MECHANISM OF REFERRED PAIN

The main cause of referred pain is ***convergence of peripheral and visceral pain fibres on the same spinothalamic neurons*** that project to the high centres in the brain (in addition to plasticity in the CNS). It is explained by the **conversion projection mechanism** (figure 11) as follows : Pain stimuli from a diseased viscus excite the spinothalamic neurons at a certain segment of the spinal cord, which then discharge to the brain. However, pain is projected to the somatic area from which the sensory nerves enter the same spinal segment. This is because normally the brain does not receive signals from the viscera, and it is even *unaware of their existence.*

** In addition to the referred pain, local pain is usually also felt at the site of the diseased viscus *due to involvement of the parietal peritoneum.* However,

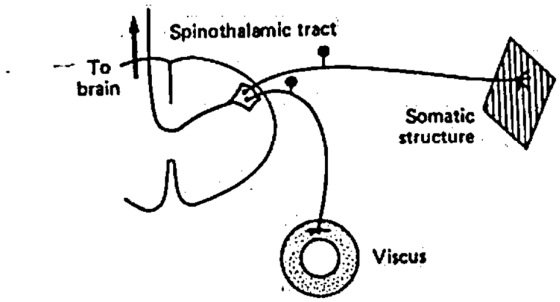


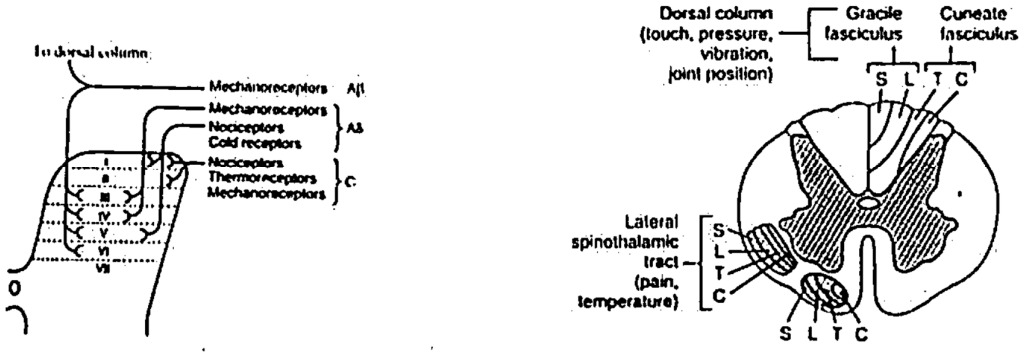
Figure 11 : The convergence projection mechanism of referred pain.

sometimes, *referred pain only is evident* while the original visceral pain is absent (e.g. cardiac pain may be presented only by pain in the left arm).

PROTOPATHIC AND EPICRITIC SENSATIONS

(1) Protopathic (primitive) sensations : These are *crude sensations* that are *perceived at a subcortical level* (*mainly at the* ***thalamus***). They include *gross movements of joints, crude pain and tactile sensations and extremes of temperature.* These sensations are *diffuse, require strong stimuli to be elicited and are exaggerated* (which is called ***thalamic hyperpathia***).

(2) Epicritic (cortical) sensations : These are *fine sensations* that are perceived at the ***sensory cortical areas*** e.g. *tactile localization and discrimination, stereognosis and fine grades of temperature.* These sensations are *well localized, not exaggerated and require no strong stimuli to be elicited.*



(a) (b)

Figure 12 : (a) The laminae at the dorsal horn of gray matter in the spinal cord (b) Arrangement of nerve fibres in the various ascending tracts.

THE SENSORY PATHWAYS (ASCENDING TRACTS)

Each sensory pathway consists of **(1)** The afferent nerves which have their cell bodies in the *dorsal root ganglia and terminate at the various laminae of the dorsal horn of the gray matter* (figure 12 a) **(2)** Second order neurons *that start at the dorsal horns and form bundles called the ascending tracts,* which terminate at *subcortical centres.* Some sensations require *third order neurons* that transmit signals to centres in the cerebral cortex. Depending on position in the spinal cord, there are ***2 systems of the ascending tracts*** called ***the anterolateral and the dorsal column (or lemniscal) systems.***

(A) THE ANTEROLATERAL SYSTEM

This system consists of the ***lateral and ventral spinothalamic tracts*** which consist mainly of types A delta and C nerve fibres. These tracts conduct signals from the ***opposite side*** (figure 13) and its fibres are arranged in the spinal cord *with the fibres from the sacral region are most superficial while those from the cervical region are most deep* (figure 12 b) .

The ventral (anterior) spinothalamic tract

This tract transports ***crude touch & pressure as well as the itch & tickle sensations.*** Its pathway consists of the following 3 neurons (figure 13) :

First order neurons : These are *A-delta and C afferent nerve fibres.* They enter the spinal cord *via the dorsal roots* and terminate in *the upper 4 laminae of the dorsal horn* (figure 12 a).specially at the ***main sensory nucleus***

Second order neurons : These constitute the tract. They start in the dorsal horn, *cross to the opposite side,* ascend in the anterior column of the spinal cord, and terminate in the ***ventro-basal thalamic complex,*** specially at the ventral posterolateral nucleus (***VPLN***).

Third order neurons : These start in the thalamus, pass in the sensory (= thalamic) radiation in the ***posterior limb of the internal capsule*** and terminate at the cortical sensory areas in the ***postcentral gyrus*** (page 120).

The lateral spinothalamic tract

This tract transmits ***pain, thermal and sexual sensations.*** It consists of 2 tracts. which are the following :

(1) The paleo-spinothalamic tract

This tract transports ***slow pain and crude thermoreceptive sensations.*** Its pathway consists of the following 2 neurons :

First order neurons : These are mainly *type C afferent nerve fibres.* They enter the spinal cord via the dorsal roots, ascend or descend a few segments in the ***Lissauer's tract*** then terminate in the *upper 3 laminae of the dorsal horn* specially at the ***substantia gelatinosa of Rolandi*** **(= SGR)** which occupies lamina II and part of lamina III.

Second order neurons : These constitute the tract, They start at the SGR, ***cross to the opposite side close to the central canal,*** ascend in the lateral column of the spinal cord and ***terminate at the following sites*** (where the transported sensations are perceived) : *The reticular formation, the periaqueductal gray area in the midbrain and the nonspecific thalamic nuclei* (specially the intralaminar nuclei) in addition to other subcortical centres.

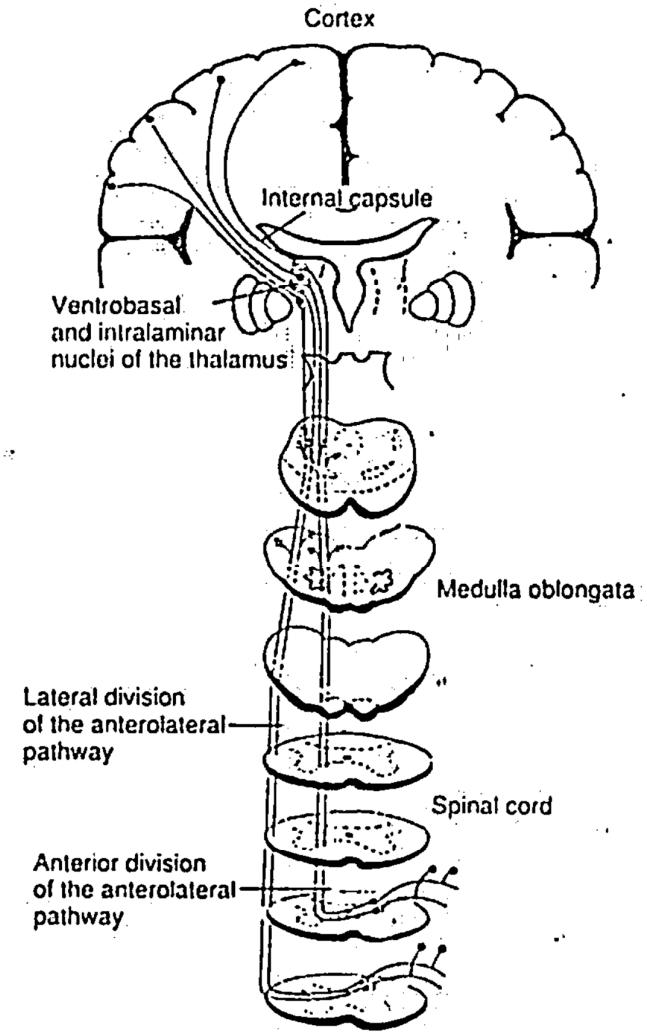


Figure 13 : The anerolateral system of ascending tracts.

(2) The neo-spinothalamic tract

This tract transports *fast pain and fine thermoreceptive sensations*. Its pathway consists of the following 3 neurons (figure 13) :

First order neurons : These are mainly *A-delta afferent nerve fibres*. They ascend or descend in the ***Lissauer's tract*** and finally terminate mainly at *laminae I and V of the dorsal horn* (figure 12 a).

Second order neurons : These constitute the tract. They start at the dorsal horns, *cross to the opposite side* and ascend in the lateral column of the spinal cord. In the brain stem, they combine with the paleospinothalamic and ventral spinothalamic tracts forming the **spinal lemniscus**, and together with the fibres of the ventral spinothalamic tract, these fibres finally terminate at the ***thalamic VPLN*** (figure 13).

Third order neurons : These are similar to those of the ventral spinothalamic tract (see above).

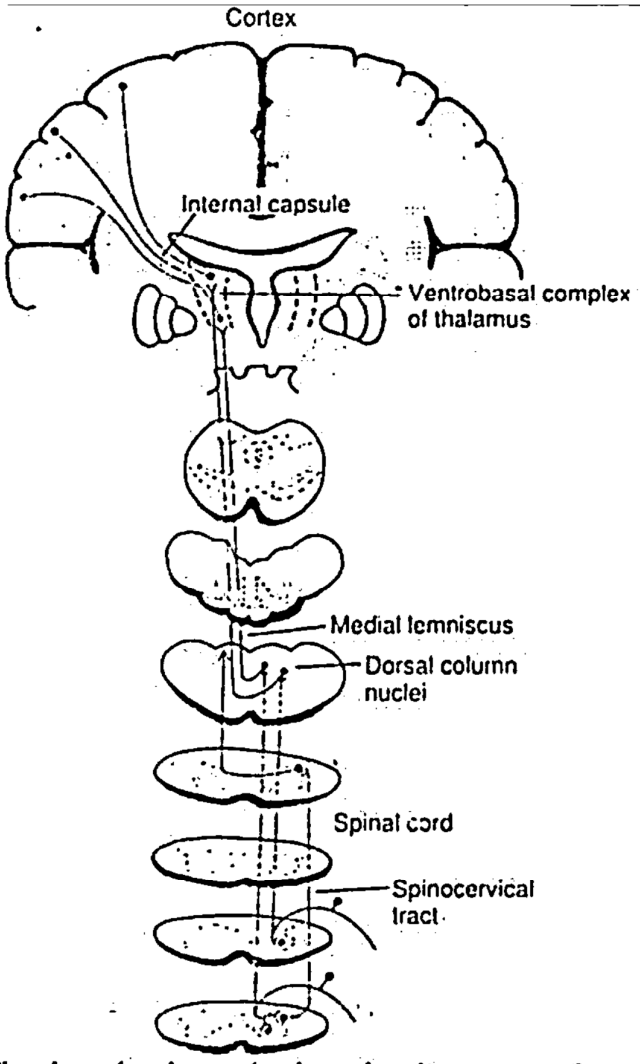


Figure 14 : The dorsal column (or lemniscal) system of ascending tracts.

(B) THE DORSAL COLUMN (or LEMNISCAL) SYSTEM

This system includes the ***gracile and cuneate tracts as well as the spinocervical tract*** (figure 14) and it consists mainly of ***types A-alpha and A-beta nerve fibres.*** It transmits mainly ***fine sensations from the same side.***

The gracile and cuneate tracts

These tracts transport **(1)** *Fine tactile sensations* (tactile localization and tactile discrimination) and also crude touch to some extent **(2)** *Stereognosis and texture of material sensation* **(3)** *Fine pressure and muscle tension sensations* **(4)** *The vibration sense* **(5)** The *proprioceptive and kinesthetic sensations* The pathways of these tracts consist of 3 neurons (figure 14) **:**

First order neurons : These are mostly type ***A-beta afferent nerve fibres.*** They enter the spinal cord and divide into medial and lateral branches (figure 12 a). The medial branch turns upwards in the ***ipsilateral dorsal column*** and ascends ***without relay as the gracile and cuneate tracts*** till relaying at the ***gracile and cuneate nuclei in the medulla oblongata*** (figure 14).

** The *gracile tract carries sensations from the lower part of the body and lies medially in the dorsal column*, while the *cuneate tract carries sensations from the upper part of the body and lies laterally* (figure 12 b).

** The neurons that form the lateral branch synapse with neurons in laminae III, IV, V and VI of the dorsal horn (figure 12 a) from which some fibres *reenter the dorsal column* and some form the *spinocervical and spinocerebellar tracts*, while other fibres *elicit certain spinal reflexes*.

Second order neurons : These start at the gracile and cuneate nuclei in the medulla, cross in the ***sensory decussation*** to the opposite side (in which the fibres are called the ***internal arcuate fibres***), then they ascend as the **medial lemniscus,** and finally they terminate at the thalamus in the **VPLN.**

Third order neurons : These start at the thalamic VPLN and terminate at the cortical sensory areas in the postcentral gyrus.

** Some fibres called ***external arcuate fibres*** arise from the gracile and cuneate nuclei and enter the cerebellum via the ***inferior cerebellar peduncle***.

HEADACHE

This is a painful sensation at the head that is ***referred*** from other structures, and its causes are either ***intracranial or extracranial*** in origin.

(A) Extracranial causes of headache

(1) Eye diseases e.g. glaucoma (due to rise of the intraocular pressure) and hypermetropia (due to persistent contraction of the ciliary muscle), which cause retro-orbital or peri-orbital headache.

(2) Teeth diseases associated with toothache.

(3) Sinusitis : The headache may be retro-orbital or in the forehead (in case of the frontal sinus) or in the face (in case of the maxillary sinus).

(4) Otitis media and otitis externa.

(5) Prolonged emotions and tension (psychogenic headache) partly due to spasm of the muscles attached to the scalp and occiput..

(B) Intracranial causes of headache

The ***intracranial pain sensitive structures*** include **(a)** The venous sinuses **(b)** The blood vessels of the meninges specially *the middle meningeal artery* **(c)** The dura at the base of the brain **(d)** The tentorium cerebelli.

Irritation of the supra-tentorial pain-sensitive structures initiates signals that are transmitted by *the trigeminal nerve* (leading to frontal headache), while irritation of the infra-tentorial structures initiates signals that are transmitted by the *second cervical nerve* (leading to occipital headache).

The brain tissue itself is insensitive, and the commonest causes of intracranial headache include the following :

(1) ***Meningeal irritation*** by inflammation (= *meningitis*), tumours, alcohol and ***constipation*** by toxic products absorbed from the colon (*although some authors believe that constipation headache is due to rectal distention*).

(2) ***Lowering of CSF pressure*** : Removal of only about 20 ml of the CSF *by a lumbar puncture needle* causes severe headache specially in the upright position due to stretch and distortion of the various dural surfaces.

(3) ***Distention of the intracranial arteries*** e.g. in fevers, hypertension (which causes throbbing headache) and ***migraine***. The latter has a genetic tendency and it occurs more in females commonly following prolonged tension or emotions as follows : These conditions lead to reflex V.C. of the cerebral arteries, which results in ischemia, and this is followed by intense V.D. that causes the headache.

The pain control analgesia system

This is a specific system that blocks pain transmission in the CNS (figure 20). Its **major constituents** include the following :

1. ***The periventricular nuclei*** in the hypothalamus.
2. ***The periaqueductal gray area*** **(PAG)** in the midbrain and upper pons.
3. ***The raphe magnus nucleus*** **(RMN)** in the lower pons and upper medulla.
4. ***A pain inhibitory complex*** **(PIC)** in the dorsal horns of the spinal cord.

Certain cortical areas are also involved in the pain analgesia system (specially the ***limbic association areas***), and the principal mediators in this system are the ***opioid peptides*** (see next).

THE OPIOID PEPTIDES

These are ***morphine-like neurotransmitters that are naturally formed in the body*** (so they are called the ***own body's morphines***). Morphine (the active substance in opium) is a potent analgesic substance that produces its effect by binding to specific ***opiate receptors*** in the nervous system. Similarly, ***the opioid peptides are analgesic substances that act by binding to the opiate receptors***. The most important opioid peptides include the following :

(1) Enkephalins : These are 2 types, ***met-enkephalin*** and ***leu-enkephalin***. They are present in all parts of the analgesia system, and are degraded by 2 types of enkephalinase enzymes (A and B).

(2) Endorphins : These are several types, the commonest of which is ***beta-endorphin***. Their analgesic effect is more stronger than that of enkephalins.

(3) Dynorphins : Like endorphins, these are several types and their analgesic effect is stronger than that of enkephalins. However, they are normally present in minute amounts in the CNS.

The opiate receptors

These are *5 types*, and they are specially present in the ***analgesia system and on the central endings of the pain-conducting nerve fibres at the dorsal horns***. They can be stimulated both ***exogenously*** (by morphine) and ***endogenously*** (by the opioid peptides).

Mechanism of pain control by the analgesia system

The analgesia system produces its effect by ***stimulating the PIC*** (see above). The PIC consists of *short enkephalinergic neurons that terminate on the central endings of the pain-conducting afferent nerves*. The released

enkephalin binds to the opiate receptors present on these nerve endings and ***prevents the release of the pain transmitters*** (=***presynaptic inhibition***)..Pain inhibition by this mechanism occurs through the following 2 pathways :

(A) Peripheral pathway of pain inhibition (spinal inhibition)

Collaterals from the ***thick A-beta nerve fibres*** that transmit mechano-receptive sensations directly stimulate the PIC. This explains how pain is relieved by counter-irritants, mechanical stimuli (e.g. skin rubbing) and acupuncture (see below). Depending on such mechanism, severe pain can be relieved by *electrical stimulation of the thick sensory nerve fibres.*

(B) Central pathway of pain inhibition (= supraspinal inhibition)

Excitation of the hypothalamic periventricular nuclei or certain cortical areas (see above) depresses pain as follows (figure 20) :

(1) The nerve fibres from the hypothalamic or the cortical areas release ***beta-endorphin*** which stimulates the PAG.

(2) ***The PAG projects enkephalinergic neurons*** (i.e. neurons which release enkephain) that stimulate the raphe magnus nucleus (RMN).

(3) ***The RMN projects serotonergic neurons*** (i.e. neurons which release serotonin) that block pain signals through ***activating the PIC.***

It is also probable that the analgesia system can inhibit pain transmission at other points than the PIC, specially at the thalamic intralaminar nuclei and the reticular nuclei in the brain stem.

Stress analgesia

Certain stress conditions are associated with analgesia e.g. ***during the stress of a battle,*** severely-wounded soldiers frequently feel no pain till the battle is over. Such analgesia is produced by impulses discharged from the cerebral cortex and hypothalamus, which excite the ***central pathway of pain inhibition*** (see above).

Acupuncture

Acupuncture relieves pain by ***both activating the peripheral pathway of pain inhibition as well as by psychogenic excitation of the central pathway.*** Both mechanisms lead to stimulation of the PIC in the dorsal horns of the spinal cord, which blocks pain transmission by releasing enkephalins (see above). For this reason, the ***efficiency of acupuncture is increased by enkephalinase-inhibitor drugs and is decreased by morphine-antagonist drugs (e.g. naloxone) which block the opiate receptors.***

THE STRETCH REFLEX AND SKELETAL MUSCLE TONE

The stretch reflex is the contraction of a skeletal muscle in response to passive stretch. It is also called ***the myotatic or muscle spindle reflex (MSR)***

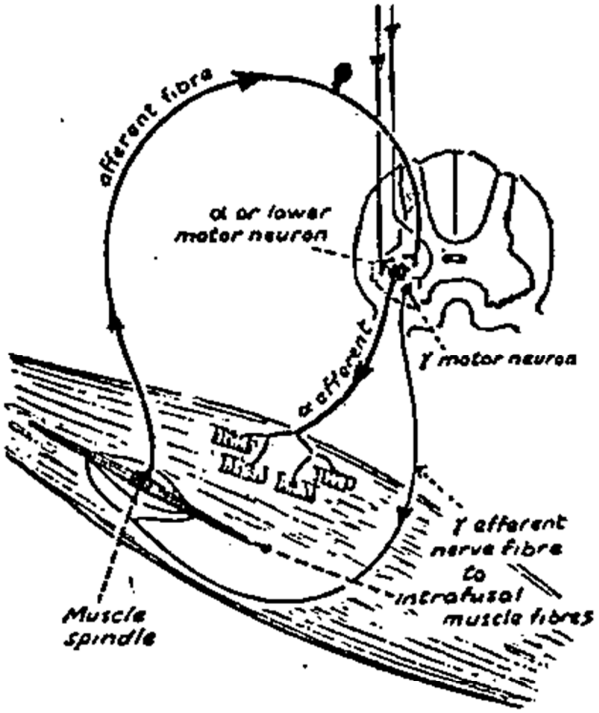


Figure 36 : Pathway of the stretch reflex (monosynaptic).Notice supraspinal control and gamma efferent nerve fibres supplying the muscle spindles.

Structure of the muscle spindle

Muscle spindles are fusiform stretch receptors present in the ***fleshy parts of skeletal muscles parallel to the muscle fibres*** which are called ***extrafusal fibres*** (figure 36). Each spindle consists of several small muscle fibres called ***intrafusal fibres*** enclosed in a connective tissue capsule that is attached to the sides of the extrafusal fibres. The ***central parts of these fibres are non-contractile*** and constitute the receptor areas of the spindles. On the other hand, their ***peripheral parts are contractile and when they contract, they stretch the central receptor areas***. There are 2 types of intrafusal muscle fibres, which are the following (figure 37) :

(1) Nuclear bag fibres : These have a ***dilated central area*** filled with nuclei and there are typically 2 of these fibres per spindle.

(2) Nuclear chain fibres : These also have multiple nuclei but they are arranged as a ***chain in the receptor area.*** They are attached to the sides of the other type, and there are 4-8 of these fibres per spindle.

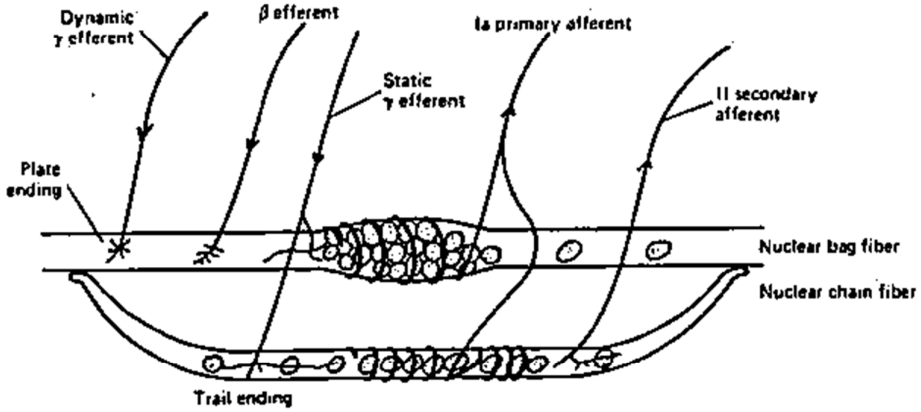


Figure 37 : The muscle spindle and its nerve supply.

Innervation (nerve supply) of the muscle spindles

(A) Afferent nerves arising from the spindles

(1) Type Ia nerve fibres : These are type ***A alpha fibres*** that are thick (average diameter 17 microns) and rapidly-conducting (velocity of conduction 70-120 meters / second). They arise from the receptor areas of ***both the nuclear bag and nuclear chain muscle fibres,*** where their endings wrap round the fibres forming ***primary*** (= ***annulo-spiral***) ***endings.***

(2) Type II nerve fibres : These are type ***A beta fibres*** that are *thinner and slower in conduction* than the Ia fibres (average diameter 8 microns). They arise from ***secondary*** (= ***flower-spray***) ***endings*** at the sides of the primary endings in the ***nuclear chain fibres only.***

(B) Efferent nerves supplying the spindles (gamma efferents)

The peripheral (contractile) parts of the intrafusal fibres are supplied by *thin myelinated* motor nerve fibres called ***gamma efferent nerves*** (= Leksell nerves). These are type ***A gamma fibres*** (having diameter 3-6 microns) that are the *axons of small anterior horn cells* called the ***gamma motor neurons*** (figure 36). They form about 30 % of the efferent nerve fibres in the ventral roots (so they are called the ***small motor nerve system***), and are 2 types :

Nervous pathway of the stretch reflex

Impulses from the muscle spindles are transmitted to the CNS by its fast-conducting afferent nerve fibres. These proceed ***directly without intervening interneurons*** to the ventral horns (figure 36) where they excite the ***alpha motor neurons*** that supply the stretched muscle (by releasing ***glutamate***). Impulses are then transmitted by the alpha motor neurons to the stretched muscle leading to contraction of its extrafusal fibres.

Therefore, the stretch reflex arc contains only ***one synapse***, and it is ***probably the only monosynaptic reflex*** in the body. Its ***reaction time*** (***or total reflex time***) is short (*19- 24 milliseconds*) and its central delay does not exceed *0.9 millisecond* (proving that it is monosynaptic).

Mechanism of stimulation of the muscle spindles

The adequate stimulus for excitation of the muscle spindles is ***stretch***, and this can be produced by either ***passive stretch of the whole muscle*** or stimulation of the ***gamma efferent fibres***. The latter cause contraction of the peripheral parts of the intrafusal fibres, which stretches their central parts and the resulting muscle contraction is said to occur via a **gamma-spindle loop**.

Function of the muscle spindles

The muscle spindles constitute a feedback mechanism that ***maintains the muscle length constant***. Elongation (stretch) of the muscle excites the muscle spindles, which leads to contraction and shortening of the muscle. On the other hand, if the muscle is shortened, the discharge of the muscle spindles decreases, which leads to relaxation and elongation of the muscle. The latter response is sometimes called ***negative stretch reflex*** (see below).

Responses of the muscle spindles to stretch

(1) Dynamic response : This occurs while the muscle length is ***increasing***, and it informs the CNS about the ***rate of change of muscle length***. It is produced mainly as a result of stretch of ***the nuclear bag fibres***. The response is an increase of the rate of discharge from the ***primary endings*** in these fibres, which is followed by a marked decrease when the new length is maintained (because these receptors are ***rapidly-adapting***).

(2) Static response : This occurs while muscle stretch is ***maintained***, and it informs the CNS about ***changes of the muscle length***. It is produced mainly as a result of stretch of ***the nuclear chain fibres***, and the response is an increase of the rate of discharge from ***the primary and secondary endings*** in these fibres, which continues as long as the new muscle length is maintained (because these receptors are ***almost non-adapting***).

THE GAMMA EFFERENT SYSTEM

FUNCTIONS OF THE GAMMA EFFERENT NERVES

Stimulation of these nerves leads to stretch of the central parts of the muscle spindles, which *increases the sensitivity of the muscles to stretch and may result in reflex muscle contraction.*

CONTROL OF GAMMA EFFERENT DISCHARGE

The gamma motor neurons are controlled by signals discharged from :

(1) Certain supraspinal areas (page 71) **:** These discharge *facilitatory and inhibitory signals through the descending tracts* (figure 36). Such discharge adjusts the stretch reflex in skeletal muscles, which is important for appropriate control of movements and posture. Also, ***anxiety is often associated with increased gamma efferent discharge*** (by supraspinal facilitatory signals), which causes exaggerated tendon jerks in anxious persons (page 69)..

(2) The skin : Noxious stimulation of the skin increases the gamma efferent discharge to the flexor muscles, which potentiates the withdrawal reflex.

(3) The skeletal muscles : Signals from skeletal muscles also increase the gamma efferent discharge as shown in the ***Jendrassik maneuver*** (page 68).

Alpha gamma linkage (or coactivation)

Whenever the alpha motor neurons are activated (whether by supraspinal signals or by impulses discharged from skeletal muscles) the gamma motor neurons are activated at the same time. The ***role of gamma efferent coactivation is to prevent relaxation of the muscle spindles during extrafusal muscle contraction, and to maintain them capable of adjusting the alpha motor neuron discharge throughout the movement.***

FUNCTIONS OF THE STRETCH REFLEX

(1) Maintenance of the erect posture against the force of gravity : This occurs through producing a ***strong muscle tone in the antigravity muscles***.

(2) Damping (smoothing) function : The signals discharged to a muscle usually have varying intensities, and this would result in incoordinated movements. However, the signals are adjusted through the *alpha-gamma linkage* so that smooth movements are produced (= ***signal averaging***).

(3) Increasing the power of muscle contraction : As a result of the *alpha-gamma linkage*, both the extrafusal and intrafusal fibres contract when a muscle is stimulated. The intrafusal fibres elicit a stretch reflex by the ***gamma-spindle loop mechanism*** (page 61), which results in a more powerful contraction of the extrafusal fibres (= **servo-assist function**).

THE SKELETAL MUSCLE TONE

DEFINITION

The skeletal muscle tone is a state of continuous mild or partial (or subtetanic) contraction of skeletal muscles ***during rest.***

MECHANISM

It is a ***static type of the stretch reflex*** (page 63) that is produced as a result of continuous mild stretch of skeletal muscles during rest by the ***series elastic elements*** present in the tendons (refer to muscle and nerve)..

DISTRIBUTION

It is present in *all skeletal muscles*, but specially in the ***antigravity muscles*** (because they are subjected to more stretch by the force of gravity). These muscles include **(1)** ***Extensors of the lower limbs*** **(2)** ***Flexors of the upper limbs*** **(3)** The ***muscles of the back and back of neck*** **(4)** The ***elevators of the lower jaw.***

FUNCTIONS OF THE SKELETAL MUSCLE TONE

(1) It is essential for maintenance of the ***erect posture.***

(2) It helps both the ***venous return and lymph flow*** from the lower limbs (against the force of gravity).

(3) The abdominal muscles' tone ***prevents visceral ptosis.***

(4) It is an ***important source of heat production***, so it is markedly increased on exposure to cold (refer to energy metabolism).

THE GOLGI TENDON ORGANS (GTOs)

These are the receptors present in the tendons of skeletal muscles (figure 38). Each GTO consists of ***a netlike collection of knobby nerve endings*** that give rise to thick myelinated type **Ib afferent nerve fibres** (which are a type of A alpha fibres) that have a diameter of about 16 microns.

A small bundle of muscle fibres is ***connected in series with each GTO,*** and the GTO is stimulated by the tension developed in that bundle. Therefore, the GTOs are ***tension receptors*** (i.e. they ***detect muscle tension***), and they are stimulated by ***both passive stretch as well as by active contraction of skeletal muscles***. They are ***slowly-adapting*** and are ***not under nervous control because they do not receive efferent nerve supply***.

Effect of stimulation of the GTOs

Signals from the GTOs excite inhibitory interneurons called ***Golgi bottle neurons*** (page 51) which produce IPSPs at both the alpha and gamma motor neurons. Therefore, such ***Golgi tendon reflex is disynaptic*** (figure 39) and leads to ***relaxation of the muscle from which it originates.***

Responses and functions of the GTOs

As in muscle spindles, the GTOs have ***dynamic and static responses***. The former occurs when the muscle tension suddenly increases and it terminates rapidly while the latter occurs when the increased tension is maintained. The main function of the GTOs is ***maintenance of a constant muscle tension*** by a ***negative feedback mechanism*** (i.e. if the muscle tension increases, the GTOs are stimulated resulting in muscle relaxation and reduction of its tension, and vice versa).

The inverse stretch reflex (autogenic inhibition)

This is ***reflex relaxation of a muscle in response to excessive stretch***. It is an inhibitory reflex that occurs if the muscle tension markedly increases. It is initiated by ***excitation of the GTOs***, and *is a protective reaction against tearing of the muscle or avulsion of its tendon from its bony attachment.*

HIGHER CONTROL OF THE STRETCH REFLEX

(A) SUPRASPINAL FACILITATORY AREAS

(1) The facilitatory reticular formation : This is a wide ***active area*** that ***discharges spontaneously by an intrinsic activity***. It is present mainly in the ***pons*** and its signals reach the spinal cord through the ***ventral reticulospinal tract***. It facilitates the stretch reflex ***mainly by activating the gamma motor neurons***, and ***almost all other facilitatory areas stimulate it***.

(2) The primary cortical motor area (area 4) : This discharges facilitatory signals to **the *alpha motor neurons through the corticospinal tract***.

(3) The vestibular and inferior olivary nuclei : These stimulate the facilitatory reticular formation and *also discharge direct facilitatory signals to* ***the alpha motor neurons*** through the vestibulospinal and olivospinal tracts.

(4) The caudate nucleus and neocerebellum : These stimulate the facilitatory reticular formation as well as the vestibular and inferior olivary nuclei.

(B) SUPRASPINAL INHIBITORY AREAS

(1) The inhibitory reticular formation : This is a small ***inactive area*** (i.e. having *no intrinsic activity*) present mainly in the ***medulla oblongata***. It is ***activated by signals from the other inhibitory areas,*** and its signals reach the spinal cord through the ***lateral reticulospinal tract,*** where they ***inhibit mainly the gamma motor neurons***.

(2) Certain cortical areas : These include mainly the ***premotor area (= area 6) and area 4 S (= main cortical suppressor area)***. These areas activate the inhibitory reticular formation both directly and through stimulating the lenticular nucleus of the basal ganglia (see below) .

(3) The red nucleus (in the midbrain) **:** This nucleus discharges ***inhibitory signals to the alpha motor neurons through the rubrospinal tract.***

(4) The lenticular (or lentiform) nucleus and paleocerebellum : These activate the inhibitory reticular formation and ***inhibit the vestibular nucleus***.

** The **main facilitatory tracts** are the *ventral reticulospinal, the vestibulospinal and the corticospinal tracts*, while the **main inhibitory tracts** are the *lateral reticulospinal and the rubrospinal tracts*. The ***reticulospinal tracts terminate at the gamma motor neurons while the other tracts terminate at the alpha motor neurons.***

. *Normally, the net effect on the alpha motor neurons is facilitatory while the net effect on the gamma motor neurons is inhibitory.* The latter effect is largely due to ***the inhibitory effect of cortical areas 6 and 4 S (which is much greater than the facilitatory effect of area 4 on the alpha neurons)***.

Polysynaptic Reflexes:

These are polysynaptic reflexes that ***require facilitation by the pyramidal system***. They include the following reflexes :

(1) The plantar reflex : Scratching the outer (lateral) edge of the sole (figure 32) by a blunt object (e.g. a key) causes plantar flexion of all toes in *normal awake adults and infants more than one year of age*. Such response is changed in many conditions into the ***Babinski's sign*** (page 82) and its centre lies in ***L_5 , S_1 and S_2 segments of the spinal cord*** (mainly the ***first sacral segment***).

(2) The abdominal reflexes : Striking the abdominal skin lightly (e.g. by a pin) leads to contraction of the underlying muscles, as indicated by movement of the umbilicus (figure 32). They are a type of the withdrawal reflex (see below), and their centres lie in ***the 7^{th} to the 12^{th} thoracic segments of the spinal cord*** (depending on the site of stimulation).

(4) The withdrawal (flexor) reflex : This is a protective powerful reflex (because it inhibits other reflexes occurring at the same time). Noxious stimulation of the skin (e.g. at a limb) leads to contraction of the flexor muscles of that limb and its withdrawal away from the stimulus (figure 33).

** The **pin is used** for eliciting the abdominal, cremasteric and flexor reflexes, in addition to ***testing of pain sensation*** and demonstration of the ***triple response*** (refer to circulation).

(5) The crossed extensor reflex : This is reflex extension of a limb during flexion of the other limb as a result of a withdrawal reflex (figure 33). It occurs with strong noxious stimuli, and is ***supportive in function***.

(7) The positive supporting reflex (reaction) : Applying pressure to the ***sole*** (e.g. the pressure exerted by the body weight during standing) leads to contraction of ***both the flexor and extensor muscles*** of the lower limbs. It is the ***only reflex that does not obey the principle of reciprocal innervation*** (page 56). Its centre extends ***from the first lumbar segment to the first sacral segment of the spinal cord***, and during standing, it renders the lower limbs to act as 2 solid pillars that support the body against gravity.

Extension of the limb occurs in the direction of pressure applied to the sole i.e. if pressure is applied to the lateral side of the sole, it leads to extension and abduction of the lower limb, while if it is applied to the medial side, it leads to extension and adduction of the lower limb.This effect has been called **the magnet reaction.**

(8) The scratch reflex : This is initiated by the sensation of itch particularly when caused by ***multiple tactile stimuli*** (e.g. the reflex initiated by a crawling insect). It can also be produced experimentally by stimulating the skin with a weak faradic current, and it results in rhythmic scratching movements to remove the irritant stimulus (and sometimes production of pain which also relieves the effect of the irritant stimulus).

THE RETICULAR FORMATION

This is a network of neurons located in the brain stem, extending *upwards to the diencephalon* (thalamus, hypothalamus and subthalamus) and *downwards to the upper part of the spinal cord* (figure 79), where it merges with its interneurons. Many nuclei and centres are present within its meshes (e.g. *the respiratory and cardiac centres, the substantia nigra, and the red, vestibular and raphe nuclei*). It is divided into **sensory and motor parts.**

(A) THE SENSORY PART OF THE RETICULAR FORMATION

This consists of small neurons that have multiple interconnections with each other (which allows for convergence, divergence and after discharge). It receives a ***rich sensory input*** (***afferent fibres***) from **(1)** All ascending lemnisci **(2)** The visual, auditory and olfactory nervous pathways **(3)** The basal ganglia **(4)** The cerebellum **(5)** The cerebral cortex (via *corticofugal fibres*) **(6)** The hypothalamus **(7)** The vestibular apparatus.

(B) THE MOTOR PART OF THE RETICULAR FORMATION

This consists of large neurons which receive signals from the sensory part and ***their axons constitute the output*** (***efferent***) ***fibres*** from the reticular formation. It contains **facilitatory and inhibitory parts :**

(1) Facilitatory (excitatory) reticular formation :

This is located mainly in the ***pons***. It has an ***inherent activity*** and the axons of its neurons divide into 2 branches :

(a) An ascending branch, which excites thre cerebral cortex, and is called the ***Ascending Reticular Activating System or ARAS*** (see below).

(b) A descending branch (= *Ventral reticulospinal tract*) which exerts a facilitatory effect on the spinal gamma motor neurons (page 71).

(2) Inhibitory reticular formation :

This is located mainly in the ***medulla oblongata***. It has ***no inherent activity***, and its axons descend as ***the lateral reticulospinal tract***, which inhibits the spinal gamma motor neurons (page 72)

then some project directly to the cerebral cortex, while the majority relay first at the ***nonspecific thalamic nuclei***, from which other fibres arise and project diffusely to ***almost all parts of the cerebral cortex*** (figure 79). The latter pathway is called the ***reticulo-thalamo-cortical pathway***.

FUNCTIONS OF THE ARAS

The ARAS ***controls the electric activity of the cerebral cortex***, and is concerned with ***consciousness and production of the alert response***, so reduction of its activity leads to sleep (see below).

FACTORS THAT AFFECT THE ACTIVITY OF THE ARAS

(A) Factors that increase the ARAS activity

(1) Sensory signals (specially pain).
(2) Signals from the cerebral cortex (via the *corticofugal fibres*) which increase alertness and resist the desire to sleep (e.g. during emotions and voluntary movements).
(3) Certain drugs called the ***analeptic drugs*** e.g. catecholamines, amphetamine and caffeine.

(B) Factors that decrease the ARAS activity

(1) Reduction of signals from the sensory pathways or the cerebral cortex.
(2) Stimulation of the sleep centres (see below).
(3) Extensive damage of the ARAS (e.g. by tumours).
(4) General anesthetic drugs : These drugs lead to unconsciousness through ***depressing the ARAS activity*** (by inhibiting the synaptic transmission between its neurons).

THE BASAL GANGLIA

The basal ganglia (BG) are subcortical masses of gray matter that include the following nuclei (figure 55) :

(1) The caudate nucleus.

(2) The lentiform (or lenticular) nucleus : This consists of 2 parts **(a)** An outer part called the **putamen (b)** An inner part called the **globus pallidas**, which is further divided into *external and internal segments.*

Both the *caudate nucleus and putamen* are called the **corpus striatum.**

(3) The subthalamic nucleus (= *subthalamus or body of Luys*).

(4) The substantia nigra (in the midbrain).

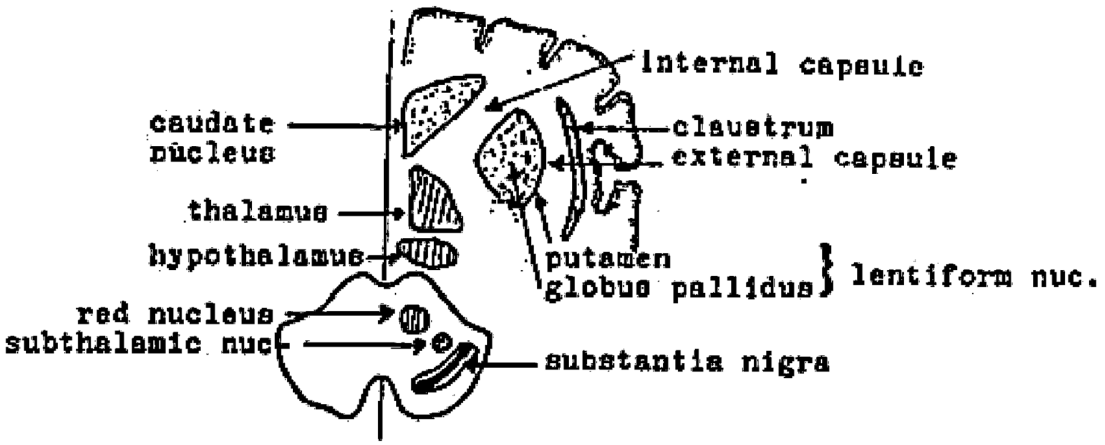


Figure 55 : The basal ganglia (BG).

CONNECTIONS OF THE BASAL GANGLIA

The BG constitute a basic part of the ***extrapyramidal system.*** *Their afferent (input) fibres are derived mainly from the cerebral cortex to the corpus striatum, while their efferent (output) fibres originate mainly from the globus pallidus.* Their connections can generally be divided into **3 parts :**

(A) Cortical connections of the basal ganglia

(1) Putamen circuit (figure 56) **:** Fibres start from the cortical motor areas and end at the **putamen,** from which new fibres arise and end at the ***internal globus pallidus.*** From the latter, fibres arise and relay at the ***thalamic ventrolateral nucleus,*** from which fibres arise and finally end at the cortical motor areas, specially ***the primary motor area (area 4).***

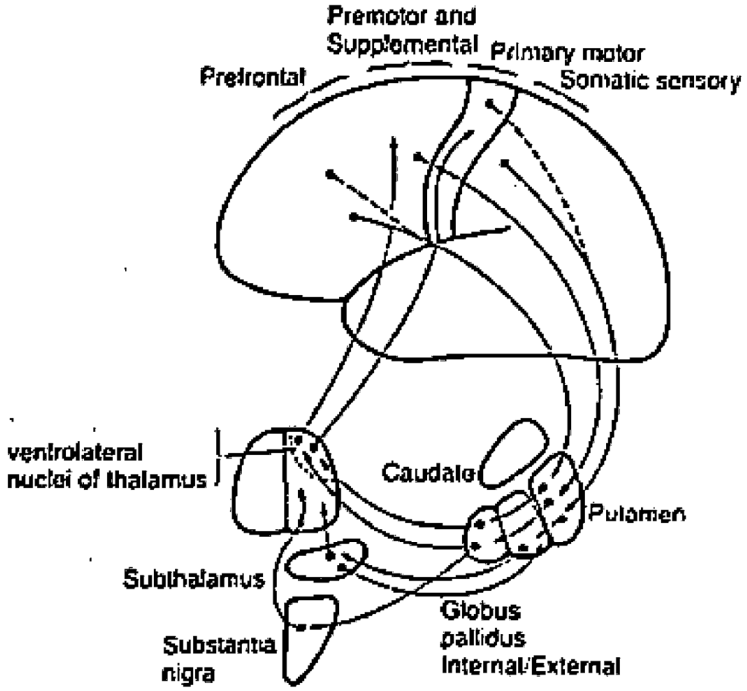


Figure 56 : The putamen circuit.

** There are other circuits that are closely associated with the putamen circuit and involve the ***subthalamus and substantia nigra*** (figure 56).

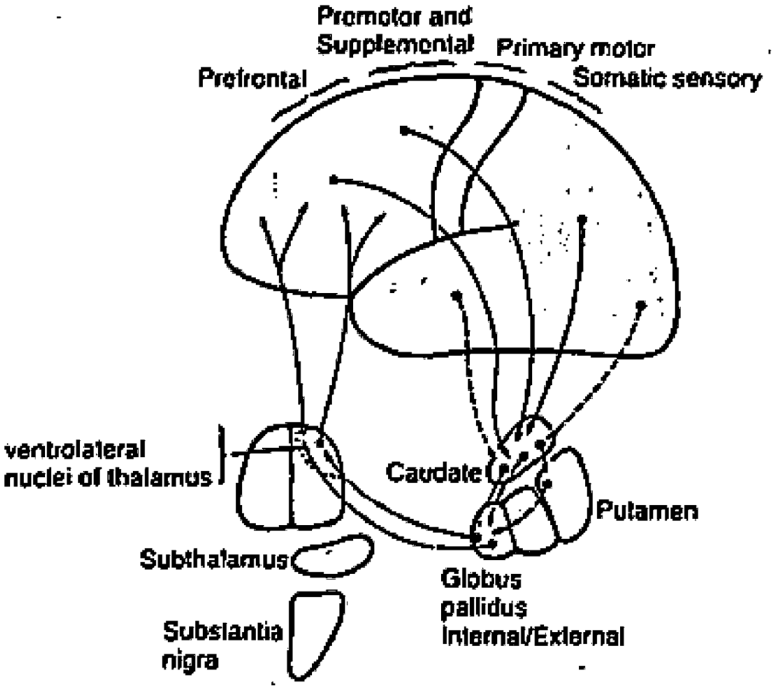


Figure 57 : The caudate circuit.

(2) Caudate circuit (figure 57) : Fibres start from both the ***cortical motor and sensory association areas*** and end at the **caudate nucleus**, from which new fibres arise and end at the ***internal globus pallidus***. From the latter, fibres arise and relay at the ***thalamic ventrolateral nucleus***, from which fibres arise and finally ***end at the cortical motor association areas.***

(B) Interconnections of the basal ganglia

(1) A negative feedback interconnection between the external part of the globus pallidus and the subthalamus (figure 56).

(2) Dopaminergic ***nigro-striatal connection*** (figure 58).

(3) GABA-ergic ***striato-nigral & striato-pallidal projections*** (figure 58).

(C) Brain stem connections of the basal ganglia

Fibres from the globus pallidus project to **(a)** ***The reticular formation*** **(b)** ***The red nucleus*** **(c)** ***The vestibular nucleus*** **(d)** ***The inferior olivary nucleus.*** Signals from the BG are transmitted *through such connections to the spinal centres via the extrapyramidal tracts.*

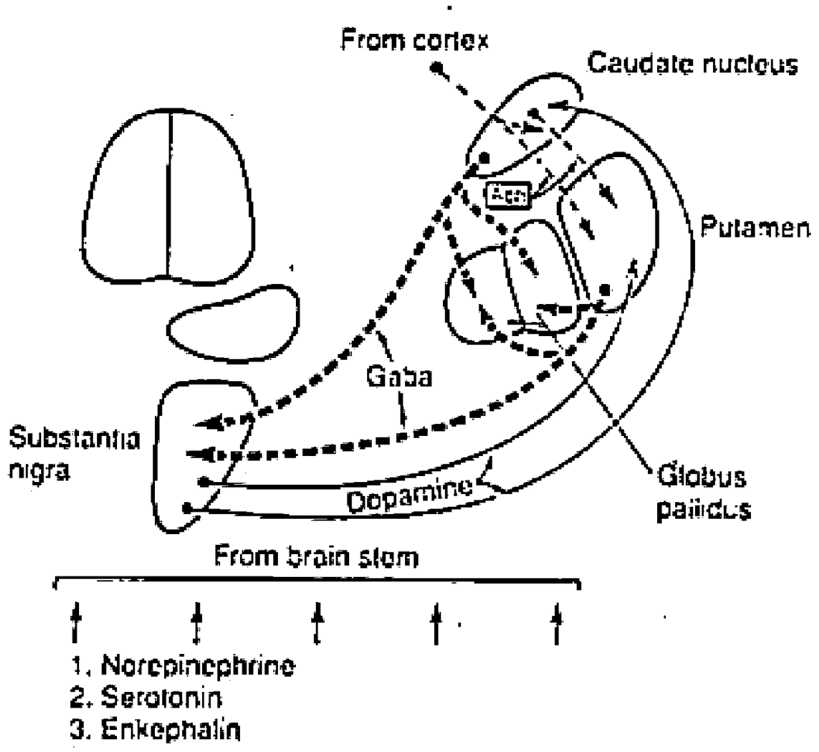


Figure 58 : Neurotransmitters in the basal ganglia.

FUNCTIONS OF THE BASAL GANGLIA

The functions of the BG are *purely motor* and include the following :

(A) Control of the muscle tone

The lentiform nucleus decreases the muscle tone by inhibiting the vestibular nucleus and activating the inhibitory reticular formation (page 72). On the other hand, *the caudate nucleus increases the muscle tone* by stimulating the facilitatory reticular formation as well as the vestibular and inferior olivary nuclei (page 71).

However, generalized stimulation of the BG decreases the muscle tone (indicating predominance of the inhibitory effect of the lentiform nucleus).

(B) Control of voluntary movements

(1) The BG discharge *before the movements start*, and are concerned with *planning and programming of movements* as follows (a) The **putamen circuit** *is concerned with execution of learned patterns of movement* (b) The **caudate circuit** *is concerned with converting thoughts into motor actions* (*a function known as the cognitive control of motor activity*). This involves determination of (i) The pattern of movements to be used and their sequence (ii) The timing and rapidity of performing the movements (iii) The scale (intensity) of movements. An example for such function is what happens to a person on seeing a lion (he automatically and rapidly turns away, begin to run and even attempt to climb a tree).

(2) As a part of the extrapyramidal system, the BG initiate sub-conscious automatic movements (e.g. swinging of the arms during walking).

DISEASES OF THE BASAL GANGLIA

(1) CHOREA

Chorea means *"dance"*, and it is 2 main types :

(a) Huntington's chorea : This is a hereditary disease, and its onset is usually at 30-50 years of age.

(b) Sydenham's chorea : This occurs in young ages (5-15 years) commonly as a complication of *rheumatic fever.*

Chorea is due to lesions of the corpus striatum, specially the *caudate nucleus.* It is associated with *degeneration of both cholinergic and GABA-ergic neurons,* and is characterized by the following symptoms :

(1) Hyperkinetic features in the form of rapid purposeless involuntary *dancing movements* that occur suddenly *during rest* and superimpose on voluntary movements. Their cause is *release of the globus pallidus and substantia nigra from inhibition* (due to GABA deficiency), which allows spontaneous discharge of excitatory signals to the cortical motor centres, resulting in such movements.

(2) Hypotonia due to loss of the facilitatory effect of the caudate nucleus on the stretch reflex. It is associated with *pendular knee jerk* (page 69).

(3) Dementia (decreased memory and cognitive function) due to loss of the acetylcholine-secreting neurons.

(2) ATHETOSIS

This is due to lesions of the *globus pallidus.* It is characterized by *hyperkinetic features* in the form of involuntary *slow writhing movements* (= twisting snake-like movements) specially in the face, the distal parts of the upper limbs and the hands

(3) HEMIBALLISMUS

This is due to lesions of the *subthalamic nucleus.* It is characterized by *hyperkinetic features* in the form of *sudden, rapid and violent involuntary movements* e.g. sudden flexion of the lower limb.

(4) PARKINSON'S DISEASE (PARALYSIS AGITANS)

This is due to lesions of the *substantia nigra,* which leads to *degeneration of the dopaminergic nigro-striatal fibres (resulting in marked reduction of the dopamine content in the BG).* It occurs more in old age (because there is normally a steady loss of the dopaminergic neurons and receptors in the BG with progress of age) and is hastened by *atherosclerosis and prolonged use of phenothiazine tranquilizers* (*which block the D_2 receptors*).

Manifestations of Parkinson's disease (Parkinsonism)

Pakinsonism is characterized by both *hyperkinetic features* (*rigidity and static tremors*) and *hypokinetic features* (*akinesia and bradykinesia*).

(1) MUSCLE RIGIDITY

This occurs in all muscles (but the *tendon jerks are usually not exaggerated*). When the limbs are passively moved, it is either continuous (= *lead-pipe rigidity*) or interrupted (= *cogwheel rigidity*). It is primarily an **alpha rigidity** (page 73) that occurs as a result of a ***release phenomenon.*** Destruction of the dopaminergic neurons releases the corpus striatum from the inhibitory effect of dopamine, and this leads to increased output of excitatory signals to the cortical motor areas, which consequently discharge excess excitatory signals to the spinal alpha motor neurons via the cortico-spinal tract resulting in rigidity.

(2) AKINESIA OR HYPOKINESIA (LACK OF MOVEMENTS)

This is associated with **bradykinesia** (= slow movements), and is manifested by **(a)** *Marked difficulty in initiating voluntary movements* **(b)** ***Mask face*** due to lack of facial expression **(c)** ***Slow, monotonous and low-volume speech*** **(d)** ***Shuffling gait*** i.e. walking rapidly in short steps without lifting the legs from the ground **(e)** ***Absence of the associated movements*** e.g. swinging of the arms during walking..

The real cause of akinesia is unknown. However, recently it was found that ***dopamine is also decreased in the limbic system***, and this might greatly reduce the psychic drive for motor activity which leads to akinesia.

(3) STATIC TREMOR

This is a tremor that appears **during rest** and disappears during sleep and on doing voluntary movements. It occurs at a rate of *3-6 or 8 cycles per second* due to regular alternating contraction of the antagonistic muscles (probably as a result of *oscillation of activity in the feedback circuits after loss of their inhibition caused by dopamine deficiency*). It is marked in the upper limbs, and in the hands it often appears as ***pill-rolling movements***.

Treatment of Parkinsonism

The main disorder in Parkinsonism is the ***imbalance between the inhibitory and excitatory influences in the BG, with predomination of the latter.*** Accordingly, the symptoms of this disease can be relieved by one or more of the following :

(1) Anticholinergic drugs (which decrease the excitability effect of acetylcholine). However, these drugs have proved not very effective.

(2) Increasing the dopamine content of the BG by either :

(a) L-Dopa : This drug ***can cross the blood-brain barrier*** and is converted to dopamine in the brain (***dopamine itself is useless because it fails to cross the blood-brain barrier***). However, its effect disappears after prolonged use.

(b) L-Deprenyl : This is a drug that ***inhibits the monoamine oxidase enzyme*** (which destroys dopamine), so it increases the dopamine content in the basal ganglia.

(c) Implantation of dopamine-secreting tissue *in or near* the basal ganglia (the best was found to be ***from a fetal corpus striatum***).

(3) Blocking the feedback circuits between the basal ganglia and the cortical motor areas : This has been tried surgically by **destruction** of either **(a)** The ventrolateral nucleus of the thalamus **(b)** The interenal segment of the globus pallidus (= ***pallidotomy***) **(c)** The subthalamic nucleus.

THE THALAMUS

The thalamus is a subcortical mass of gray matter located at the *lateral wall of the third ventricle*. It contains the following nuclei :

(A) Nonspecific projection nuclei

These include mainly the *middle and intralaminar nuclei*. They receive signals from the *reticular formation and discharge to almost all areas of the cerebral cortex*.

(B) Specific projection nuclei

(1) Ventro-posterior nucleus (VPN) : Its lateral part **(VPLN)** receives the ***spinal and medial lemnisci*** while its medial part **(VPMN)** receives the ***trigeminal lemniscus***, and both parts then project to the cortical sensory areas in the postcentral gyrus.

(2) Lateral geniculate body : This projects ***visual impulses*** to the occipital lobe (refer to the visual pathway in special senses).

(3) Medial geniculate body : This projects ***auditory impulses*** to the temporal lobe (refer to the auditory pathway in special senses).

(4) Ventrolateral nucleus (= thalamic motor nucleus) : This receives signals from both the ***cerebellum and the basal ganglia***, and projects to the ***cortical motor areas*** (playing a major role in the control of motor functions).

(5) Anterior nucleus : This receives signals from the ***hypothalamus*** and discharges to the *cortical limbic lobe*.

(6) Dorsomedial and dorsolateral nuclei : These are ***association nuclei*** that receive signals from other thalamic nuclei, then the *dorsomedial nucleus projects to the prefrontal cortical area*, while the *dorsolateral nucleus projects to the cortical association areas*.

FUNCTIONS OF THE THALAMUS

(1) The thalamus conveys all sensations to the cerebral cortex *except olfaction (smell)* because its nuclei are ***relay stations*** in the pathways of **(a)** Epicritic sensations from the opposite side (the VPN) **(b)** Visual signals (the lateral geniculate body) **(c)** Auditory signals (the medial geniculate body).

** *Recently, it was reported that part of the olfactory sensation also relays in the thalamus.*

(2) The intralaminar and middle nuclei are the centre for perception of protopathic (crude) sensations and slow pain from the opposite side.

(3) The thalamus is a relay station for signals from the ***contralateral cerbellum and ipsilateral basal ganglia*** to the cortical motor areas (through the lateral ventral nucleus).

(4) The nonspecific projection nuclei are relay station in the ***ascending reticular activating system*** (= ARAS, page 133).

(5) The thalamus is a part of the systems concerned with **(a)** ***Recent memory and emotional reactions*** (through its connections with the hypothalamus and limbic lobe, page 129) **(b)** ***The high intellectual functions*** (through its connections with the cortical association areas) **(c)** The ***behaviour and personality*** (through its connections with the prefrontal cortical areas).

THE THALAMIC SYNDROME

This is a disease that results from thrombosis of a branch of the posterior cerebral artery called the ***thalamogeniculate artery*** (which supplies a large part of the thalamus, specially its lateral and posteroventral parts). It leads to the following manifestations **in the opposite side of the body :**

(1) Early in the disease, there is complete loss of all sensations. The ***facial sensations are usually less affected*** because the damage occurs mainly in the VPLN (while the VPMN is little affected).

(2) The loss of kinesthetic sensations results in ***sensory ataxia*** (page 113) as occurs in tabes dorsalis (page 32).

(3) Within the next few weeks or months, protopathic (= crude) sensations recover (page 21). This is accompanied by ***emotional disturbances,*** and although the threshold of pain is elevated, yet it is accompanied by an exaggerated central effect called ***thalamic hyperpathia***. The latter is a ***release phenomenon*** that occurs due to facilitation of the intralaminar and middle nuclei (probably as a result of interruption of the signals that activate the analgesic brain areas, page 35).

(4) The epicritic (= fine) sensations are permanently lost resulting in loss of both tactile localization and discrimination as well as ***astereognosis.***

(5) Damage of the ***ventrolateral nucleus*** **(=** ***thalamic motor nucleus*****)** leads to the following :

(a) Loss of the cerebellar control on the cortical motor areas, which results in ***asthenia*** (= muscle weakness or paresis), ***hypotonia*** and manifestations of ***cerebellar ataxia*** (page 112).

(b) Interruption of the ***connections between the basal ganglia and the cerebral cortex*** may result in abnormal movements similar to those occurring in ***chorea and athetosis*** (page 101).

** In the thalamic syndrome, the **ataxia is mixed** i.e. it is both sensory and motor (page 113) due to loss of the kinesthetic sensations as well as the cerebellar control on the cortical motor areas

THE HYPOTHALAMUS AND LIMBIC SYSTEM

The hypothalamus is a part of the ***diencephalon*** located below and anterior to the thalamus. *It is a main component, and the major output pathway of the limbic system, so their functions are closely interrelated* (see below). It contains the **following groups of nuclei** (figure 51) :

(1) Anterior group (supraoptic, suprachiasmatic, preoptic and paraventricular nuclei).

(2) Lateral group (mainly a large lateral nucleus).

(3) Medial group (dorsomedial and ventromedial nuclei as well as the arcuate nucleus).

(4) Posterior group (posterior nucleus and the mamillary bodies).

(5) Periventricular nuclei (refer to the analgesia system, page 35).

FUNCTIONS OF THE HYPOTHALAMUS

The hypothalamus is essential for **homeostasis** through the following :

(1) Control of autonomic functions : The anterior nuclei control parasymp. functions while the posterior and lateral nuclei control symp. functions.

(2) Control of the endocrine system : This occurs by 2 ways :

A- Nervous control : The hypothalamus controls 2 endocrine glands by sending nerve signals **(a)** ***The adrenal medulla*** (through affecting the vasomotor centre) **(b)** ***The posterior pituitary gland*** (through the ***hypothalamo-hypophysial tract***). The hormones of this gland (ADH and oxytocin) are also synthesized in the hypothalamus.

B- Hormonal control : The hypothalamus controls the anterior pituitary gland (and consequently most other endocrine glands) by releasing the ***hypophysiotropic hormones*** from its *median eminence* (refer to endocrines).

(3) Regulation of body temperature : The hypothalamus contains *sensitive thermoreceptors* as well as the *thermoregulatory centre*. The latter consists of a ***heat loss centre*** in the anterior nuclei and a ***heat gain centre*** in the posterior nuclei (see in energy metabolism).

(4) Control of water balance : This occurs by the hypothalamic ***osmoreceptors***, which regulate both water intake and water loss as follows :

(a) Water intake : This occurs through affecting activity of the ***thirst centre***, which leads to drinking when stimulated e.g. in cases of dehydration.

(b) Water loss : This occurs through adjusting release of ***ADH*** from the posterior pituitary gland, which controls the urinary water loss.

(5) Control of food intake : This occurs by activity of the ***hypothalamic appestat centre***, which is subdivided into 2 parts :

(a) A feeding centre in the lateral nuclei : This centre is continuously active. Its stimulation increases the appetite and its damage causes ***anorexia***.

(b) A satiety centre in the ventromedial nucleus : Stimulation of this centre decreases the appetite by inhibiting the activity of the feeding centre, while its damage increases the appetite and leads to ***hyperphagia***.

The appestat also has a ***glucostatic function*** e.g. in hypoglycemia, the satiety centre is inhibited, and this increases the activity of the feeding centre.

(6) Control of circadian (=diurnal or 24 hours) rhythms : This occurs by the ***suprachiasmatic nuclei***, which are the pacemakers for the circadian rhythms in the body (e.g. the rhythms in the secretion of *ACTH and melatonin*, the *sleep-wake cycles and the body temperature rhythm*). These nuclei receive signals from the eyes (via the *retino-hypothalamic fibres*) and their function is to synchronize the various body rhythms to the 24-hour light-dark cycle (but the mechanism remains unknown).

(7) Regulation of sexual functions : The hypothalamus regulates release of ***GTHs***, which control spermatogenesis and ovulation as well as the secretion of sex hormones from the gonads. This is shown by the ***ovulation reflex*** (= *a*

(10) Emotional expression (reactions) : Emotions may be associated with either ***excitation*** e.g. rage (anger) or ***worry*** e.g. depression, anxiety and fear (see below). The expression of emotions involves activity of (a) The pre-frontal lobe (b) The hypothalamus (c) The limbic system (page 95).

THE LIMBIC SYSTEM

This system consists of 2 components :

(1) The limbic lobe of the cerebral cortex : This is a rim of primitive cortical tissue around the hilum of the cerebral hemispheres. It is also called the ***rhinencephalon*** and it contains mainly the ***cingulate and hippocampal gyri*** in addition to the *uncus, the piriform and entorhinail cortex* (figure 52).

(2) Certain subcortical structures : These include the ***amygdaloid nuclei, hippocampus, hypothalamus, fornix, anterior thalamic nucleus, septal nuclei and upper part of the midbrain*** (= ***limbic midbrain area***).

Connections of the limbic system

(1) Between its different parts, specially between the hypothalamus and the amygdaloid nucleus via the ***stria terminalis*** (figure 53).

(2) A few connections with the neocortex.

(3) The **Papez circuit** (figure 53) **:** The hippocampus is connected via the fornix to the mamillary bodies, and these are connected via the mamillo-thalamic tract to the anterior thalamic nucleus, which projects to the cingulate gyrus, and this finally discharges to the hippocampus again.

FUNCTIONS OF THE LIMBIC SYSTEM

(1) Perception of **olfactory (smell) sensation.**

(2) Control of the feeding behaviour : This is one of the functions of the ***amygdaloid nuclei*** Its stimulation causes chewing and licking movements while its damage causes severe hyperphagia (to food and other objects).

(3) Control of autonomic functions : Many limbic structures control autonomic effects (specially changes in the blood pressure and respiration).

(4) Control of sexual behaviour : The behaviour that accompanies the sexual act is regulated in the limbic system particularly ***the amygdaloid nuclei,*** since bilateral damage of these nuclei ***in males*** leads to abnormal sexual behaviour together with hypersexuality.

(5) Memory and learning (pages 127 and 128)

(6) Control of emotions : Together with the hypothalamus, the limbic system controls the emotional reactions. Stimulation of the ***amygdaloid nuclei*** can produce fear or rage (page 93) while their damage produces placidity &

(7) Plasticity and learning :

This means changes in the strength of synaptic transmission (which represent forms of ***learning & memory***, page 129). Such changes are ***presynaptic and postsynaptic***,and they include **potentiation, depression & sensitization**

Synaptic potentiation (or facilitation)

This is production of high-amplitude EPSPs in response to stimulation. It occurs after a brief period of *rapidly repeated stimulation of the presynaptic neuron* (= tetanizing train of stimuli), and is 2 types :

1- Short-term potentiation (= post-tetanic potentiation)

This lasts up to one minute, and is due to accumulation of excess Ca^{2+} in the presynaptic knobs as a result of the repeated stimulation (which increases the release of the neurotransmitter, and in turn increases the EPSP).

2- Long-term potentiation (LTP)

This specially occurs in the ***hippocampus*** where the excitatory transmitter is ***glutamate***. It lasts a few hours or days, and ***both the pre and postsynaptic neurons participate in its production***. The presynaptic neuron releases glutamate which increases Ca^{2+} influx in the postsynaptic neuron, thus increasing the EPSP. The postsynaptic neuron in turn releases a chemical signal (? NO) that causes more glutamate secretion from the presynaptic neuron.

Synaptic depression

This is a decrease in the response of postsynaptic neurons, and is 2 types :

1- **Habituation** : This is a ***gradual decrease of the postsynaptic response*** when a stimulus to the presynaptic neuron is repeated over and over. It is due to *less release of the neurotransmitters from the presynaptic terminals secondary to reduction of the intracellular* Ca^{2+} (which occurs as a result of closure of the Ca^{2+} channels by an unknown mechanism).

2- Long-term depression (LTD) : This is the opposite of LTP, and is produced by slower stimulation of the presynaptic neurons (which is associated with a smaller rise of the Ca^{2+} content in the postsynaptic neuron).

LEARNING

(A) Non-associative learning

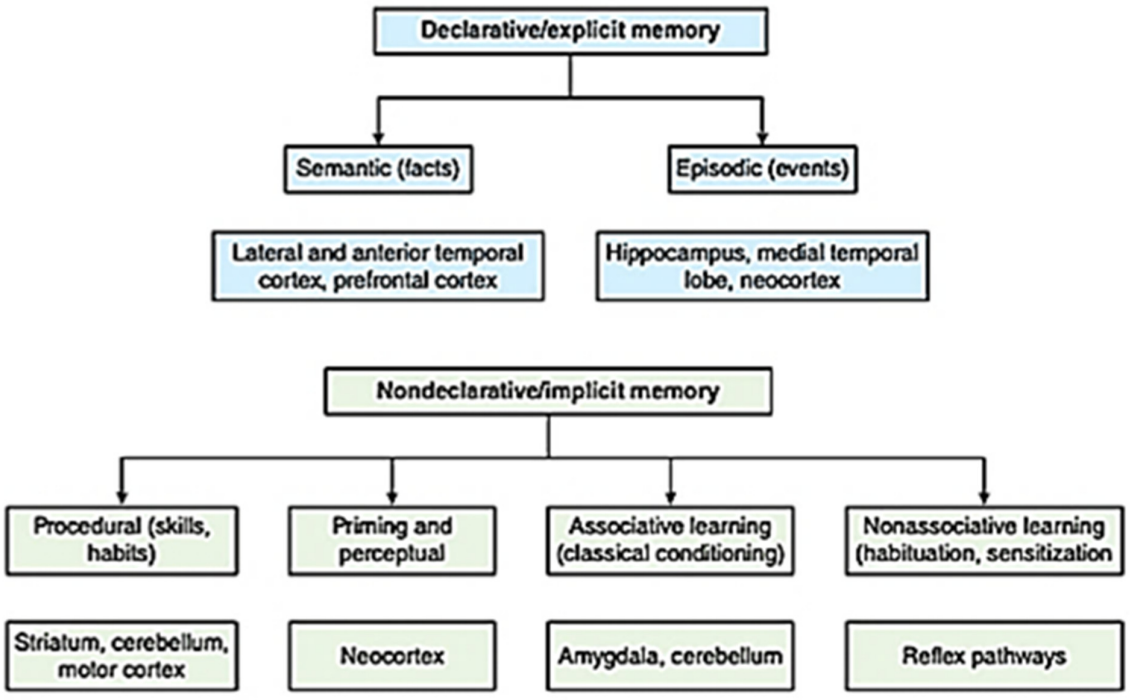
This is learning about ***a single stimulus that is repeated many times.*** There is 2 forms of this type :

(1) Habituation : This is a gradual decrease in the response to a particular stimulus when repeated. This learns the individual to ignore a large number of nonsignificant stimuli (so it is considered a ***negative memory***). It is due to a decrease in Ca^{2+} in the nerve endings that mediate the response (page.42)

(2) Sensitization : This is potentiation of the response to a particular stimulus when repeated (so it is considered a ***positive memory***). It occurs if the stimulus is coupled once with an unpleasant (or a pleasant) stimulus. It is due to prolongation of the action potential in nerve endings.(page 43)

(B) Associative learning

This is learning by ***pairing of stimuli***, and the best example in this case is learning through **conditioned reflexes.** In such reflexes, the subject is learned to respond to stimuli that normally do not produce responses. These stimuli are called ***conditioned stimuli*** **(CS),** while the stimuli that normally produce the response are called the ***unconditioned stimuli*** **(US).**



There are 2 main types of memories :

(A) **Implicit (reflexive) memory** (= memory of which the person is *unconscious or unaware*). It includes (1) *Associative and nonassociative learning* (see above) (2) *Learned skills* (= *skill memory*) (3) *Habits* (e.g. *driving cars becomes a habit by training and occurs automatically without need for conscious recall of information*) (4) *Priming* (= *facilitation of recognition of words or objects by previous exposure to them*).

(B) **Explicit or declarative memory** (= *conscious recall of information*) which includes the following types :

(1) **Short-term (primary or recent) memory :** This is memory that lasts a few seconds to a few minutes (or at most a few hours) then fades away unless it is converted to long-term memories..

(2) **Long-term (secondary or remote) memory :** This is memory that lasts for long times (*years and may be for the whole life*).

CONSOLIDATION OF MEMORY

This is the conversion *of short-term memory into long-term memory*. It requires 5-10 minutes for minimal consolidation and 1- 4 hours for more strong consolidation. Therefore, *short-term memory is vulnerable during the first 5 minutes* (i.e. it is liable to be erased) if disrupted by external stimuli such as anesthesia, electroshock or hypothermia.

Mechanism of consolidation

This is produced (and also accelerated and potentiated) by *rehearsal of the short-term memory* i.e. repitition of the information in mind again and again (so consolidation is reduced in mentally-fatigued persons). It involves *protein synthesis in neurons* (so drugs and antibiotics that inhibit protein synthesis do not affect short-term memory but prevent its consolidation).

THE MEMORY TRACES

Memories are stored in the brain through *facilitation of synaptic transmission*. The facilitated (or new) pathways are called **memory traces**, and once they are established, they can be activated by the mind to reproduce the memories. They can occur at all levels of the nervous system but *particularly in the cerebral cortex*.

New informations are first *processed in the hippocampus*, and what proves to be significant is *codified into specific classes* that will be *consolidated then stored in association with other memories of the same type*. This is *necessary to search for various memories when required*.

THE CEREBELLUM

Anatomically, the cerebellum (CB) consists of 3 lobes separated by 2 deep transverse fissures **(a)** A small anterior lobe **(b)** A large posterior lobe **(c)** ***A flocculonodular lobe*** (located posteroinferiorly). The anterior and posterior lobes on either side constitute ***2 large hemispheres,*** which are separated by a narrow band called the ***vermis*** (figure 59 A).

3 pairs of peduncles connect the cerebellum to the brain stem (the superior peduncle to the midbrain, the middle peduncle to the pons, and the inferior peduncle to the medulla oblongata)

FUNCTIONAL (PHYSIOLOGICAL) DIVISIONS OF THE CB

From the functional point of view, the anterior and posterior lobes are organized along their ***longitudinal axes,*** and the CB is divided into 3 parts :

(1) Vestibulocerebellum (= archicerebellum) : This is the oldest part of the CB, and it consists mainly of the *flocculonodular lobe*.

(2) Spinocerebellum (=Intermediate or paleo-cerebellum) : This consists of the intermediate zones of the 2 hemispheres and most of the vermis.

(3) Cerebrocerebellum (= Lateral or neo-cerebellum) : This is the newest part of the CB. It consists of the large lateral zones of the 2 hemispheres.

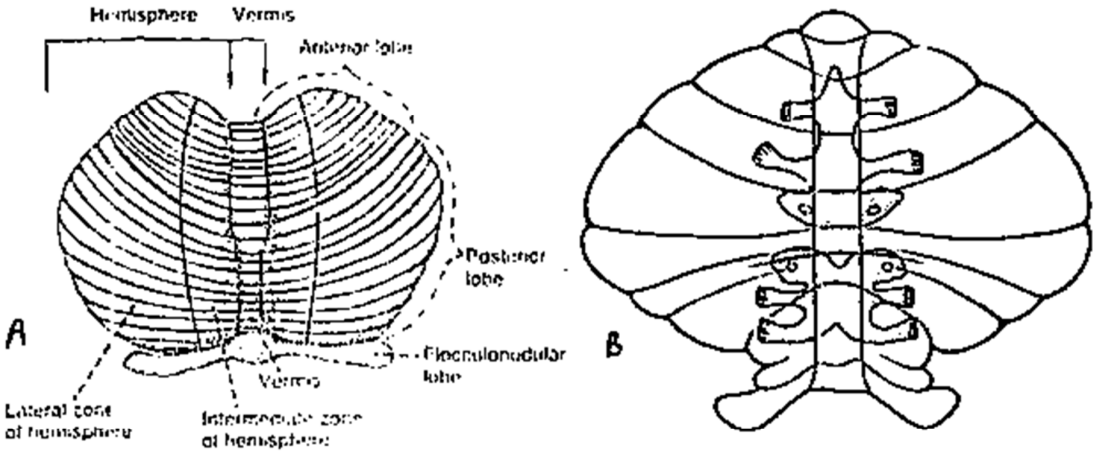


Figure 59 :(A) Functional parts of the CB (B) Topographical representation.

The various parts of the body are ***topographically represented*** in the CB. The axial parts of the body lie in the vermal part, while the limbs and facial regions lie in the intermediate zones. Also, the body is represented upright in the posterior lobe and upside down in the anterior lobe (figure 59 B).

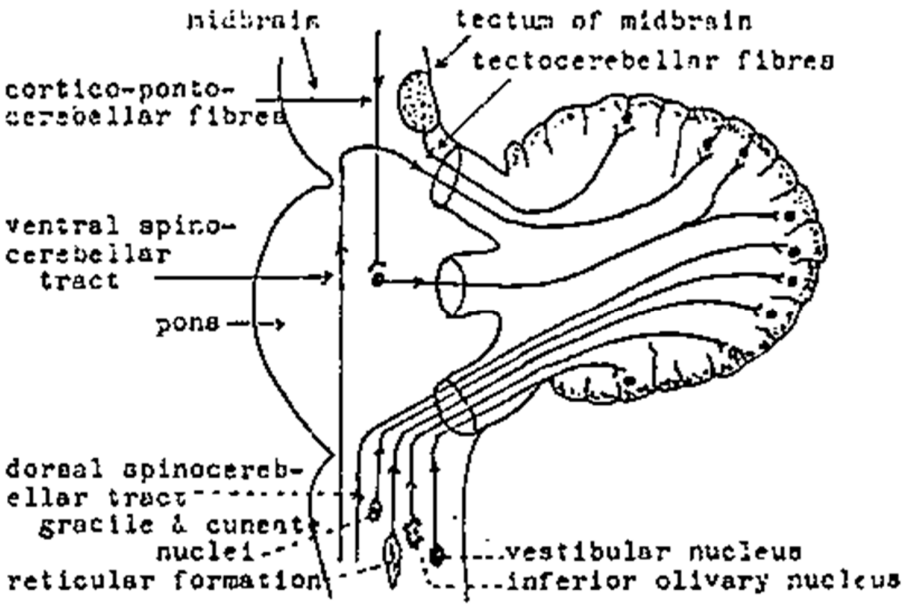


Figure 60 : Afferent (input) nerve fibres to the cerebellum.

CONNECTIONS OF THE CEREBELLUM

The CB has an external layer of gray matter (= ***cerebellar cortex***), and an inner layer of white matter. In the latter, there are **3 deep nuclei (a)** ***Dentate nucleus*** laterally **(b)** ***Fastigial nucleus*** medially **(c)** ***Interpositus nucleus*** (formed of the ***globose and emboliform nuclei***) between the other 2 nuclei.

Both the afferent and efferent connections of the CB pass through the ***3 cerebellar peduncles*** (= ***CPs***). *The afferent nerve fibres relay first at the cerebellar cortex*, then the latter discharges to *the deep nuclei from which the efferent nerve fibres originate and leave the CB* (figure 63).

AFFERENT (INPUT) NERVE FIBRES TO THE CB

The CB receives both *sensory and motor informations* as follows (figure 60)

(A) Through the superior CP, the CB receives fibres from :

1. ***The tectum of the midbrain*** (= the superior and inferior colliculi), which transmits visual and auditory signals to the CB.
2. ***The ventral spinocerebellar tract***, which terminates in the ***spinocerebellum*** and informs about the signals that reach the spnal motor neurons from the cortical motor areas (= *efference copy*, page110).

(B) Through the middle CP, the CB receives few fibres from the reticular formation, but mainly fibres from the ***contralateral motor areas of the cerebral cortex*** via the **cortico-ponto-cerebellar pathway** (figure 62).

(C) Through the inferior CP, the CB receives fibres from :

1. ***The inferior olivary nucleus*** (to all parts of the CB).

2. ***The vestibular apparatus*** (both directly and via the vestibular nuclei) mainly to the flocculonodular lobe.
3. ***The reticular formation*** (mainly to the vermis)
4. ***The dorsal spinocerebellar tract***, which transmits signals from ***proprioceptors*** that inform the CB about performance of movements (page 110).
5. ***The gracile and cuneate nuclei*** : The fibres that arise from these nuclei are called ***external arcuate fibres*** (page 25) and they also transmit proprioceptive signals to the CB.

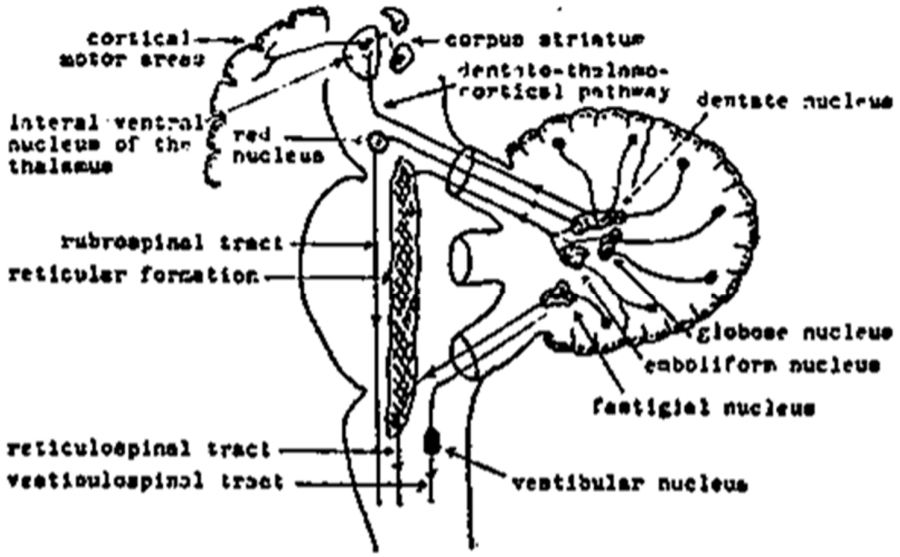


Figure 61 : Efferent (output) nerve fibres from the cerebellum.

EFFERENT (OUTPUT) NERVE FIBRES FROM THE CB

There are 3 efferent pathways from the 3 parts of the CB (figure 61) :

(A) From the vestibulocerebellum : Fibres from this part relay at the ***fastigial nucleus***, from which efferent fibres arise and pass through the ***inferior CP*** to the ***vestibular nuclei and reticular formation*** (then to the spinal motor neurons via the *vestibulospinal and reticulospinal tracts*).

(B) From the spinocerebellum : Fibres from this part relay at the ***nucleus interpositus***, from which efferent fibres arise and pass through the ***superior CP*** to **(1)** ***The opposite ventrolateral thalamic nucleus***, then to the *opposite cortical motor areas* **(2)** ***The red nucleus***, then to the spinal cord via the rubrospinal tract **(3)** ***The reticular formation*** in the upper part of the brain stem, then to the spinal cord via the reticulospinal tract.

(C) From the cerebrocerebellum : Fibres from this part relay at the ***dentate nucleus***, from which efferent fibres arise and pass through the ***superior CP*** to the ***opposite ventrolateral thalamic nucleus***, then to the opposite cortical motor areas (= ***cerebello-dentato-thalamo-cortical pathway***).

** Each cerebellar hemisphere is connected to the **contralateral cerebral cortex** by both afferent and efferent fibres, which constitute ***a neuronal circuit*** that starts and ends in the cerebral cortex. This circuit is called the ***cortico-ponto-cerebello-dentato-thalamo-cortical circuit*** (figure 62).

** Since each cerebellar hemisphere controls the ***contralateral cortical motor areas***, then it is clear that the cerebellum exerts its effects mostly ***on the same side of the body*** (because almost all fibres of the pyramidal tract cross to the opposite side).

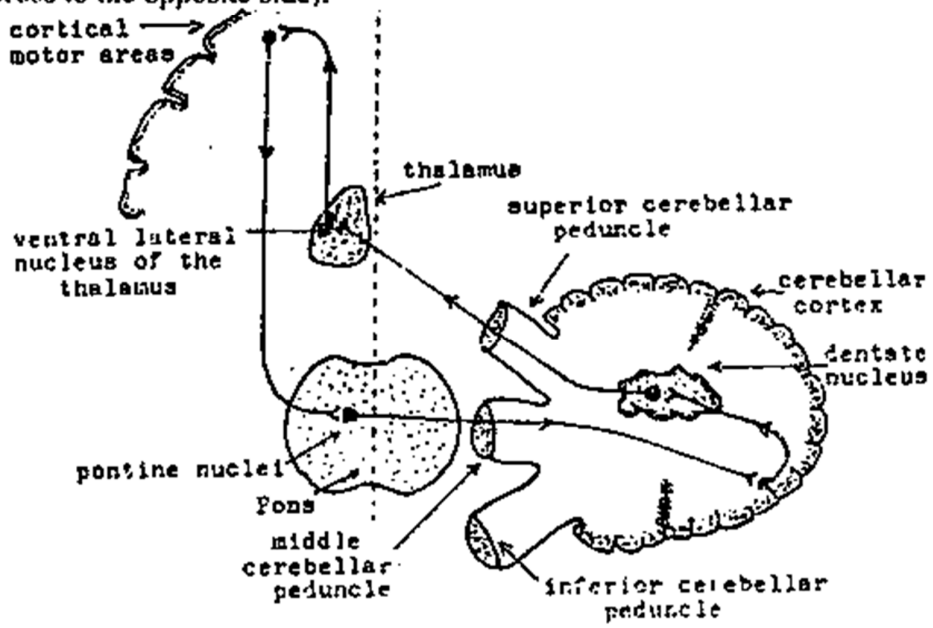


Figure 62 : The cortico-ponto-cerebello-dentato-thalamo-cortical circuit.

STRUCTURE OF THE CEREBELLAR CORTEX AND ITS NEURONAL CIRCUITS

The cerebellar cortex (figure 63) is formed of 3 layers **(1) Molecular layer** that contains *parallel interconnecting fibres* as well as 2 types of cells called ***basket and stellate cells*** (not shown in figure 63) **(2) Purkinje cell layer (PCs),** the axons of which are *the only fibres that leave the cerebellar cortex* **(3) Granule cell layer** that contains ***granular cells***.

The afferent fibres entering the CB are divided into 2 groups :

(A) Climbing fibres : These are afferent fibres from the ***inferior olivary nucleus***. They excite both the *deep nuclear cells* (DNCs) as well as the PCs.

(B) Mossy fibres : These include ***all other afferent fibres*** that enter the CB + some fibres from the inferior olivary nucleus. They excite both the DNCs and the ***granule cells***, the axons of which then ***excite the PCs as well as the basket & stellate cells***. The latter 2 cells cause ***lateral inhibition of the adjacent PCs*** which *sharpens the output signals from the CB* (page 50)

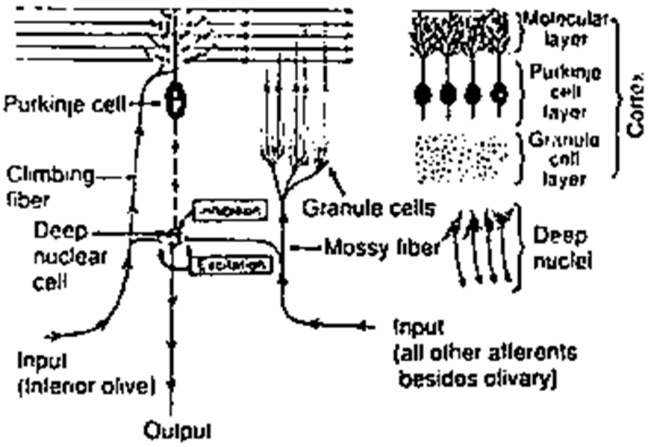


Figure 63 : The cerebellar cortex and the climbing and mossy fibre circuits.

FEATURES OF THE CEREBELLAR NEURONAL CIRCUITS

(1) The inhibitory neurons in the CB release **GABA** while the excitatory neurons release **glutamate.**

(2) ***The PCs continuously fire inhibitory signals to the DNCs.*** However, the excitatory effect of the climbing and mossy fibres on the DNCs normally predominates, so during rest the ***DNCs continuously fire excitatory signals.***

(3) The circuits contain ***no reverberators****, so normally there is no afterdischarge and the effects of cerebellar stimulation are transient.*

(4) The mossy fibre circuit *sharpens the input signals to* the CB through ***lateral inhibition of the adjacent PCs*** (see above).

Functions of the mossy fibre circuit

This circuit helps **precise execution of voluntary movements** as follows : A *copy* of the signals discharged from the cortex to perform a certain movement is conducted to the CB via the pontine mossy fibres (the *cortico-ponto-cerebellar pathway*). These signals stimulate the DNCs, which discharge *excitatory* ***"turn on "*** *signals* that help ***initiation of the movement.*** At the end of the planned movement, the PCs would have been excited by the granule cells, so they send *inhibitory* ***"turn off "*** *signals* to the DNCs, which thus stop discharging. This mechanism has been called **negative feedforward inhibition**, and it leads to relaxation of the muscles (which helps ***termination of the movement without overshooting or oscillation***).

Functions of the climbing fibre circuit

This circuit is important for ***learning the CB to perform new patterns of movement.*** *The inferior olivary nucleus* receives informations about **(1)** the

intended movement (from the motor cortex) (2) the performed movement (from the contracting muscles). It *compares both informations*, and if there was **mismatch** (which usually occurs when a new pattern of movement is performed for the first time), its firing rate is modified leading to a ***change in the sensitivity of the PCs***. If the new movement is repeated over a period of time, such change in the sensitivity of the PCs (plus other possible cerebellar processes) will learn the CB to perform such movement coordinately.

FUNCTIONS OF THE CEREBELLUM

The cerebellum is concerned with ***subconscious control of motor activity***. Its functions as well as the involved parts include the following :

(A) CONTROL OF EQUILIBRIUM AND POSTURAL MOVEMENTS

This is the function of the vestibulocerebellum. It receives information from the ***vestibular apparatus***, then through the ***fastigial nucleus***, it discharges to the brain stem, and through the vestibulospinal and reticulospinal tracts it controls equilibrium and postural movements by affecting the activity of the ***axial muscles*** (= trunk and girdle muscles).

Trunk ataxia : This results from lesions of the vestibulocerebellum. It is characterized by equilibrium disturbances (the patient sways on standing, he cannot maintain the erect posture and walks by a staggering or drunken gait)

(B) CONTROL OF THE STRETCH REFLEX

The ***cerebrocerebellum exerts a facilitatory effect*** on the stretch reflex and increases the muscle tone (page 71), while the ***spinocerebellum exerts an inhibitory effect*** (page 72). However, normally ***the facilitatory effect predominates*** so *cerebellar disease often results in hypotonia* (see below).

(C) CONTROL OF VOLUNTARY MOVEMENTS

(1) ROLE OF THE SPINOCEREBELLUM

(1) Comparing function : When a movement is performed, the spinocerebellum receives 2 informations (figure 64) **(a)** *Signals from the motor cortex* (via the cortico-ponto-cerebellar pathway) that inform about the intended plan of movement (= ***afference copy***) **(b)** *Feedback signals from the periphery* via the spinocerebellar tracts. The ventral tract informs about the cortical signals that reach the spinal motor neurons (= ***efference copy***, page 105) while the dorsal tract informs about performance of movements (page 106).

The spinocerebellum ***compares all these informations***, and if there is an error in performance, it sends ***signals from the nucleus interpositus*** to the *motor cortex, red nucleus and reticular formation.* These areas send corrective signals that control the activity of the spinal motor neurons, resulting in adjustment of the performance to match the intention, which leads to coordinated movements specially of the hands and fingers. Such function is ***aided by the climbing fibre circuit*** (page 108).

(2) Damping function : Almost all movements are ***pendular*** (due to momentum) so they have a tendency to overshoot. However, the spinocerebellum prevents this by ***subconscious signals*** that stop the movement at the intended point. Such damping effect is produced by contraction of the antagonistic muscles through the *cerebellar stretch reflex* (page 109).

If the CB was damaged, the ***cerebral cortex can consciously recognize the overshoot*** and it then initiates a movement in the reverse direction by contraction of the antagonistic muscles. However, this movement also overshoots, and is corrected again by overshooting cortical signals. This process is repeated, so the arm oscillates back and forth for several cycles before it finally settles at the intended point (= ***kinetic, intention or action tremor***).

(3) Coordination of ballistic movements : Ballistic movements are those which occur very rapidly (e.g. the fingers during typing, and the eyes during reading) and for this reason, the above comparing coordinating function cannot operate. They are ***pre-planned*** to go specific distances then stop, and this is also coordinated by the spinocerebellum aided by the ***turn on / turn off signals of the mossy fibre circuit*** (page 108).

(2) ROLE OF THE CEREBROCEREBELLUM

(1) Planning of movements : The cerebrocerebellum is informed about the desired movement ***before it starts*** (via the cortico-ponto-cerebellar pathway). The basal ganglia receive a similar information (page 100) and both provide the plan of execution of the movement.

(2) Prediction of movements : The cerebrocerebellum ***predicts the next movement at the same time a present movement is occurring***. This function is necessary for smooth transition from one movement to the next (thus joining the sequential movements and preventing decomposition).

(3) Timing of movements : The cerebrocerebellum also provides appropriate timing for each succeeding movement. This function ***determines when the next movement should begin***, so its absence causes the succeeding movement to begin too early or too late, resulting in incoordination of the movement (specially rapid movements e.g. writing, running and talking).

Extramotor predictive function of the cerebrocerebellum

The cerebrocerebellum can predict events *other than movements*, specially the rates of progression of auditory and visual stimuli e.g. a person can predict from a changing visual scene how rapidly he is approaching an object.

THE NEOCEREBELLAR SYNDROME

The manifestations of neocerebellar disease are **ipsilateral**, and include :

(A) Hypotonia : This is due to loss of the facilitatory effect on the stretch effect, and is associated with a ***pendular knee jerk*** (page 69).

(B) Asthenia (= muscle weakness) : This is due to difficulty in initiation of muscle contraction caused by loss of the function of the mossy fibre circuit (page 108).

(C) Motor ataxia : This is incoordination of voluntary movements, *specially the rapid movements*. Its manifestations include the following :

(1) Dysmetria : This is inability to control the distance of a motor act, which may either overshoot the intended point (= *hypermetria or pastpointing*) or stops short before it (= *hypometria*).

(2) Kinetic (intention or terminal) tremor : This is an oscillatory movement that appears on performing movements (specially at their end) but is *absent at rest*. It is due to *cortical correction of the overshoot* (page 111).

(3) Rebound phenomenon : This is overshooting of a limb when a resistance to its movement is suddenly removed. It is well demonstrated by the *arm pulling test* (figure 65 a), in which the patient may hit his face by his forearm after release of the resistance that is exerted by the examiner.

(4) Asynergia : This is loss of the harmony between the various groups of muscles involved in performance of voluntary movements, which results in decreased ability to perform smooth and coordinated movements.

(5) Failure of progression of movements : This is manifested by **(a)** ***Adiadochokinesia*** i.e.inability to perform rapidly alternating opposite movements e.g. repeated pronation and supination of the hands (figure 65 b) **(b)** ***Decomposition*** **(= *fragmentation*)** ***of movements*** i.e. performing the movement in steps and not as a continuous act.

(6) Dysarthria : This is difficulty in producing clear speech. The syllables may be too long or too short (resulting in jumbled vocalization), and speech may also become ***staccato or scanning*** (i.e. cut off into separate syllables).

(7) Nystagmus : This is a tremor of the eyeballs that occurs on fixing the eye at an object placed at one side of the head (page 144).

(8) Staggering (or drunken) gait : The patient walks unsteadily and on a wide base (= ***zigzag-like gait)*** in a drunken (swaying) manner, and tends to fall on the diseased side.

ATAXIA

This means ***incoordination of voluntary movements***, and it is either ***sensory or motor*** (***sometimes mixed in the thalamic syndrome***, page 90).

(A) Sensory ataxia : This occurs as a result of lesions (or diseases) of the proprioceptive sensory pathways, commonly in the dorsal column of the spinal cord (= the gracile and cuneate tracts). It specially occurs in **(1)** ***Tabes dorsalis*** (page 31) **(2)** ***Subacute combined degeneration*** (page 33) **(3)** ***Polyneuritis*** (page 32) **(4)** ***Thalamic syndrome*** (page 90) **(5)** ***Chronic alcoholism*** **(6)** ***Friedreich's ataxia*** (a hereditary disease that causes degeneration of the dorsal and lateral columns of the spinal cord).

The **manifestations (features) of sensory ataxia include (a)** Loss of dorsal column sensations (page 24) **(b)** ***+ve Romberg's sign*** (page 32) **(c)** Inability to walk in the dark **(d)** Difficulty in walking at day light. There is a ***stamping gait*** (= *high steppage gait* with a slap when the foot reaches the floor), and the patient walks at a broad base and *always looks at his feet.*

The following table shows the differences between sensory and motor ataxia

	SENSORY ATAXIA	MOTOR ATAXIA
Most common cause	Tabes dorsalis	Neocerebellar disease
Gait	High steppage (stamping gait)	Staggering (drunken gait)
Romberg's sign	Positive	Negative
Effect of vision	Corrected by vision	Not affected by vision
Deep sensations	Impaired or lost	Normal
Tremors	Absent	Kinetic tremors present
Nystagmus	Absent	Present
Speech	Normal	Scanning or staccato

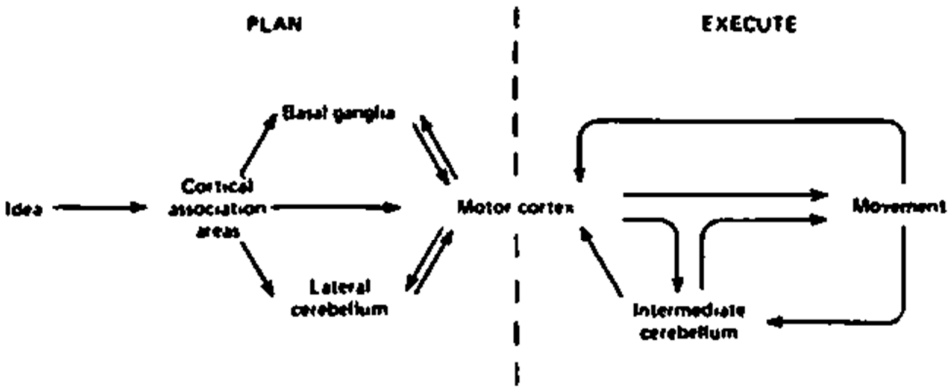


Figure 71 : Planning and execution of voluntary movements.

THE DESCENDING (MOTOR) TRACTS

The descending tracts can be classified into 2 systems known as the ***pyramidal and extrapyramidal systems.*** The neurons of these tracts are called ***upper motor neurons,*** and they terminate at the spinal motor neurons which are called the ***lower motor neurons.***

	PYRAMIDAL SYSTEM	EXTRAPYRAMIDAL SYSTEM
Origin	Cortical only	Cortical (much wider) and extracortical
Tract	Mononeuronal	Multineuronal
Pathway	Direct activation pathway	Indirect activation pathway
Crossing	About 90%	About 50 %
Termination	Cranial nerve nuclei and alpha neurons in the spinal cord	Alpha and gamma neurons in the spinal cord only (not at the cranial nuclei)
Location	Medullary pyramids, and in lateral column of spinal cord mainly	Outside the medullary pyramids, and in lateral and ventral columns of spinal cord
Time of function	Only after the first year of life	During and after the first year of life
Function	Initiates fine skilled voluntary movements and increases the muscle tone	Initiates gross and associated movements, decreases the muscle tone and controls autonomic functions

The medial and lateral motor systems

The medial motor system includes *the ventral corticospinal tract and the vestibulospinal and reticulospinal tracts*. These tracts terminate at the ***medial portions of the anterior horns***, and they control the ***muscles of the trunk*** (= ***axial muscles***) ***and proximal portions of the limbs***. This system is concerned with **(a)** Stabilization of the pelvic and shoulder girdles to maintain posture and equilibrium **(b)** Production of a postural background for performance of fine movements **(c)** Control of gross and automatic movements

The lateral motor system includes the *lateral corticospinal tract and the rubrospinal tract*. These tracts terminate at the ***lateral portions of the anterior horns***, and they control the ***distal muscles of the limbs*** which perform fine discrete (= skilled) movements specially in the fingers and hands.

(1) UPPER and LOWER MOTOR NEURON LESIONS

An UMNL results from damage of the cortical motor areas or anywhere along the course of their descending tracts, commonly in the ***internal capsule*** due to cerebral hemorrhage or thrombosis. On the other hand, a LMNL results from either damage of the spinal (or cranial) motor neurons by disease (commonly ***poliomyelitis***) or injury of the motor nerves by trauma or disease (e.g. ***polyneuropathy***).

DIFFERENCES BETWEEN UMNL and LMNL

Although both lesions result in paralysis of skeletal muscles, yet each has characteristic manifestations.

(1) Extent of paralysis (widespread in UMNL and localized in LMNL).

(2) Site of paralysis : This is always at the same side in LMNL but it may be on either side in case of UMNL e.g. a hemisection of the spinal cord at the cervical region leads to ipsilateral hemiplegia, while a lesion in the internal capsule leads to contralateral hemiplegia (page 83).

(3) Recovery : UMNL does not recover because the upper motor neurons ***cannot regenerate due to absence of neurolemma***. Conversely, LMNL can recover if it is due to injury of the motor nerves (because these nerves ***can regenerate due to presence of neurolemma***), but they cannot recover if the motor nerve cells themselves are damaged (e.g. in poliomyelitis).

(4) Muscle tone : In LMNL, there is ***hypotonia or atonia*** (i.e. muscle flaccidity) due to interruption of the efferent limb of the stretch reflex.

On the other hand, in UMNL there is ***hypertonia*** i.e. muscle spasticity (= ***decorticate rigidity***) mainly in the ***antigravity muscles***. It is a type of ***gamma rigidity*** that shows the ***lengthening (clasp-knife) reaction*** (page 65). It occurs as a ***release phenomenon*** due to *damage of the extrapyramidal fibres with the pyramidal fibres while passing together in the internal capsule* (page 76), which results in ***reversed supraspinal balance on the gamma motor neurons from inhibition to excitation*** (page 72).

(5) Tendon jerks : These are lost in LMNL and exaggerated in UMNL due to the same causes of hypertonia (see above). Also, ***clonus*** (page 69) ***often appears in UMNL***, and is the most diagnostic feature of this lesion.

(6) Superficial reflexes :

(a) The *abdominal and cremasteric reflexes are lost in both lesions* due to loss of pyramidal facilitation in UMNL (page 74) and interruption of their efferent limbs in LMNL.

(b) The plantar reflex is lost in LMNL, but is modified in UMNLs and the response becomes ***dorsiflexion of the big toe and fanning of the other toes*** (probably due to interruption of the pyramidal and extrapyramidal fibres respectively). Such response is known as the ***positive Babinski's sign or the plantar extensor reflex*** (figure 49). ***However, this sign may be present in some normal individuals*** (see below).

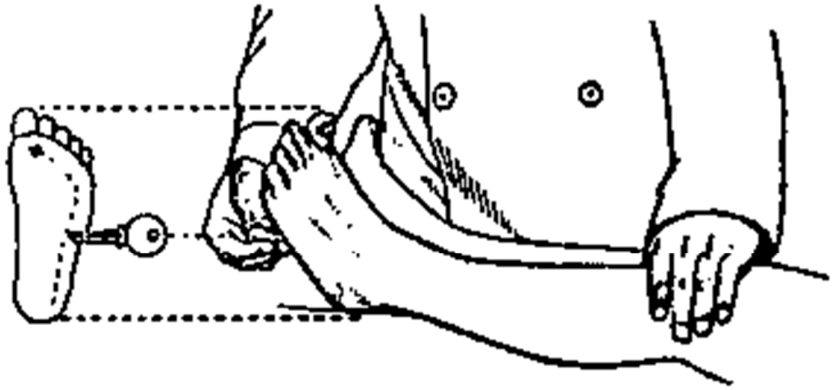


Figure 49 : A positive Babinski's sign.

(7) Tonic neck reflexes : In UMNL, turning the head towards the hemiplegic side leads to extension and abduction of the paralyzed arm, while turning the head towards the healthy side leads to more flexion and adduction of the paralyzed arm (the latter position is the posture usually acquired by the paralyzed upper limb).

(8) Muscle status : Muscle wasting (= atrophy) occurs rapidly and markedly ***in LMNL*** due to degeneration of the motor nerves that supply the muscles. On the other hand, the paralyzed muscles in UMNL are atrophied only after relatively long periods due to disuse (= ***disuse atrophy***).

(9) Response to electric stimulation : Normally, stimulation of skeletal muscles by Faradic (alternating) currents produces tetanus while their stimulation by Galvanic (direct) currents produces contraction only at the make (= closing) and break (= opening) of the circuit, whether the cathodal or the anodal electrode was used for stimulation. Therefore, in the latter condition, there are ***4 contraction states*** **(1) CCC** (= cathodal closing contraction) **(2) COC** (= cathodal opening contraction) **(3) ACC** (= anodal closing contraction) **(4) AOC** (= anodal opening contraction), and the strength of contraction was found to be as follows :

CCC > ACC > AOC > COC

In UMNL, the paralyzed muscles respond normally to both currents and their chronaxies are also normal. On the other hand, ***the response in case of LMNL is altered, and is called the reaction of degeneration*** (see next).

The following table shows the differences between UMNL and LMNL :

	UMNL	LMNL
Extent of paralysis	Widespread	Localized
Site of paralysis	Commonly contralateral	Only ipsilateral
Recovery	No recovery	Occurs if AHC are intact
Muscle tone	Hypertonia	Hypotonia or atonia
Tendon jerks	Exaggerated with clonus	Lost
Superficial reflexes	Lost + Babinski's sign	Lost
Tonic neck reflexes	Present	Absent
Muscle status	Normal (disuse atrophy in long-standing cases)	Rapid atrophy
Electric stimulation	Normal response	Reaction of degeneration

(2) EFFECTS OF LESIONS OF THE PYRAMIDAL TRACT AT VARIOUS LEVELS

Lesions of the pyramidal tract cause paralysis of the ***UMNL type below the level of the lesion***. However, the side affected and the extent of paralysis differ according to the site of the lesion as follows :

(1) IN AREA 4 : This usually leads to restricted paralysis in the opposite side e.g. ***monoplegia*** (= paralysis of one limb) because area 4 is widespread and is rarely damaged completely.

(2) IN THE CORONA RADIATA : This leads to ***contralateral monoplegia or hemiplegia*** (= complete paralysis of one half of the body), depending on the extent of the lesion.

(3) IN THE INTERNAL CAPSULE : This leads to ***contralateral hemiplegia*** in most cases because *almost all descending fibres are injured.*

	Gamma rigidity	Alpha rigidity
Cause	Increased gamma discharge	Increased alpha discharge
Muscles affected	Antigravity muscles	All muscles
Resistance to movement	Uni-directional	Bi-directional
Type of rigidity	Clasp-knife	Lead-pipe or cogwheel
Effect of velocity	Increases with velocity	Not velocity-dependent
Tendon jerks	Exaggerated and clonus may also be present	Not necessarily exaggerated
Common diseases	Upper motor neuron lesion and decerebrate rigidity	Parkinsonism

(4) HEMISECTION OF THE SPINAL CORD (= THE BROWN-SEQUARD SYNDROME)

This lesion interrupts the ascending and descending tracts on the affected side, which results in the following symptoms :

(A) ABOVE THE LEVEL OF THE LESION

Cutaneous hyperesthesia (= increased sensibility) in the ***ipsilateral dermatomes*** due to irritation of the nerve roots by the trauma.

(B) AT THE LEVEL OF THE LESION

The following effects occur ***on the same side*** :

(1) Loss of all sensations in the areas innervated by the afferent nerves that enter the damaged segments.

(2) Paralysis of the muscles supplied by the efferent nerves that arise from the damaged segments. This is a ***LMNL*** due to damage of the spinal motor neurons (i.e. the anterior horn cells).

(3) Loss of the reflexes that involve the damaged segments.

(C) BELOW THE LEVEL OF THE LESION

(1) ***UMNL in the same side*** that causes hemiplegia or paraplegia (depending on the level of the lesion) due to interruption of the pyramidal tract.

(2) ***V.D. in the same side*** due to interruption of the vasomotor tract

(3) ***Ipsilateral miosis*** (in cases of *cervical lesions only*).

(4) **Sensory disturbances :**

(a) Ipsilateral loss of fine tactile, proprioceptive, kinesthetic, pressure and vibration sensations, due to *interruption of the dorsal column tracts.*

(b) Contralateral loss of pain and temperature sensations due to interruption of the lateral spinothalamic tract that crosses from the opposite side.

** Crude touch is little affected at both sides because it is transmitted partly by the ventral spinothalamic tracts and partly by the dorsal column tracts.

(3) COMPLETE TRANSECTION OF THE SPINAL CORD

This is fatal if it was above the origin of the phrenic nerve (i.e. above the 3rd cervical segment) e.g. ***in hanging*** due to paralysis of the respiratory muscles. However, at lower levels, patients pass in 3 stages (a) ***Spinal shock*** (b) ***Recovery of spinal reflex activity*** (c) ***Failure of spinal reflex activity***.

(A) STAGE OF SPINAL SHOCK

The manifestations of this stage include the following :

(1) **Loss of all sensations** below the level of the lesion.

(2) **Quadriplegia or paraplegia** (depending on the level of the lesion).

(3) **V.D. below the level of the lesion** due to interruption of the descending

fibres from the vasomotor centre (may lead to ***hypotension*** in severe cases).
(4) Bilateral miosis *if the lesion was in the lower cervical region*, due to interruption of the descending pupillodilator fibres.
(5) Loss of spinal reflex activity below the level of the lesion *because the spinal centres at this part become functionless*. This causes **loss of :**

a- The withdrawal reflex and other superficial reflexes.

b- The stretch reflex and tendon jerks, leading to flaccidity of the paralyzed muscles (i.e. ***flaccid paralysis***).

c- The erection reflex, as well as the defecation and micturition reflexes, leading to feces and urine incontinence, and dribbling of urine (a condition known as ***retention with overflow***).

CAUSE (MECHANISM) OF SPINAL SHOCK

Spinal shock is due to ***sudden withdrawal of supraspinal facilitation on the spinal alpha motor neurons*** (page 74). It is ***not a hypotensive shock*** (as proved by presence of normal spinal reflexes above the level of the lesion), and is ***not a traumatic shock*** (as proved by the fact that a *second transection made below the first transection does not lead to a second spinal shock*).

DURATION OF THE SPINAL SHOCK

This varies directly with the ***degree of encephalization*** (= degree of development of the cerebral cortex). Accordingly, the lower the degree of encephalization, the shorter the duration of the spinal shock will be (e.g. it lasts only a few minutes in frogs and rats, 1-2 hours in dogs and cats, and several days in monkeys). On the other hand, in man (who is maximally encephalized), it lasts ***2-6 weeks***.

COMPLICATIONS OF SPINAL SHOCK

(1) Hypotension (specially in cases of high-level spinal cord lesions).

(2) Excessive protein catabolism (due to lack of movement) causing muscle wasting and bone dissolution.

(3) Ischemia of the areas compressed against bed (upper back, gluteal region and heels) so these areas are liable to ulceration (= ***decubitus ulcers or bed sores***) which heal poorly due to protein depletion.

(4) Urinary tract infection due to urine retention and stasis.

(5) Fall of the body temperature (due to reduction of the metabolic rate after loss of the muscle tone).

** Rapid recovery of the spinal reflex activity can be achieved by **(1)** ***Antibiotics*** to prevent infection in the urinary tract or bed sores **(2)** Drugs that ***stimulate the spinal centres*** **(3)** ***Bladder catheterization*** to prevent urine stasis **(4)** ***Prevention of bedsores*** by cleaning the skin with antiseptics and frequent changing of the patient's position. **(5)** ***Adequate nutrition***.

(B) STAGE OF RECOVERY OF SPINAL REFLEX ACTIVITY

After the spinal shock, the spinal centres recover gradually as follows :

(1) The flexor (withdrawal) reflex and Babinski's sign are usually the first responses to reappear, followed by the extensor reflexes e.g. the knee jerk.

(2) The static stretch reflex (muscle tone) recovers resulting in ***spastic paralysis***. It appears first in the flexor muscles (resulting in ***paraplegia in flexion***) then in the extensor muscles a few months later (resulting in ***paraplegia in extension***) accompanied by the ***positive supporting reaction***.

(3) The activity of the ***spinal vasomotor centres*** (the lateral horn cells) is restored, leading to V.C., so the arterial blood pressure rises.

(4) Reflex micturition and defecation return, but such acts are ***automatic as in infants*** (due to absence of voluntary control).

(5) Sexual reflexes recover (e.g. stimulation of the external genital organs in males leads to erection).

(6) Appearance of the MASS REFLEX : This is a hyper-reactive spinal reflex response that ***appears after a few months***. Mild noxious stimuli *applied to the skin below the level of the lesion result in widespread effects* including **(a)** *Exaggerated withdrawal of the stimulated part* **(b)** *Urination and defecation* **(c)** *V.C. and pallor with profuse sweating* **(d)** *Rise of the arterial blood pressure*. It is due to hyperexcitability of the spinal centres accompanied by ***irradiation of signals*** in the spinal cord (see below).

** Patients are trained to induce urination or defecation through producing ***intentional mass reflexes*** (by striking or pinching the skin of the thigh).

** Spinal recovery and the mass reflex may be a ***release phenomenon*** (i.e. due to release of the spinal neurons from the supraspinal gamma inhibitory control). However, it has also been attributed to ***denervation hypersensitivity*** of the spinal neurons as well as to growth of ***new collaterals*** that constitute additional excitatory endings on the spinal neurons.

(C) STAGE OF FAILURE OF SPINAL REFLEX ACTIVITY

This is a ***terminal*** (i.e. ***premortal***) ***stage*** that usually results from bad management during the recovery stage. It is often associated with ***general toxemia*** due to infection of the bed sores or the urinary tract (and the latter frequently terminates by ***uremia***).

The spinal centres below the level of the lesion become depressed again resulting in the following symptoms :

(1) Loss of the muscle tone and tendon jerks, followed by loss of the mass reflex and the withdrawal reflex then the Babinski's sign. Thus, the muscles become flaccid and the body temperature falls.

(2) Loss of the defecation and micturition reflexes resulting in constipation and ***urine retention with overflow***.

(3) ***Hypotension*** (due to depression of the spinal V.C. centres).

- **Two types of brain potentials can be recorded:**

I- Evoked potentials : The electrical events that occur in the cortex after stimulation of a sense organ can be monitored with a recording electrode.

Types of Evoked potentials :

1- Somatosensory stimuli → SSEP

2- Auditory stimuli → AEP

3- Visual stimuli → VEP

2- Spontaneous potential(Electroencephalogram)

the recording of the variations in brain potential. The EEG can be recorded with scalp electrodes through the unopened skull or with electrodes or or in the brain. The term electrocorticogram is used for the recording obtained with electrodes on the pial surface of the cortex.

(II) The Electro-encephalogram (EEG)

-The EEG is the record of the spontaneous electric activity of the brain.

-It can be recorded by applying electrodes on the scalp of patient.

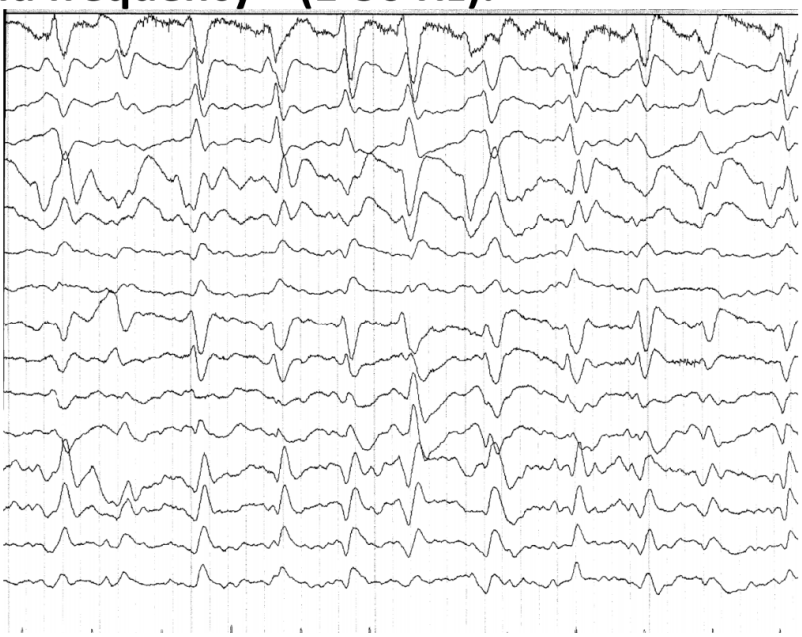
-The electric activity appears on a multi-channel recorder as waves of variable intensity (0-200 mV) and frequency (1-50 Hz).

Conditions Required :

1- Recording of EEG should be done in a calm room at a comfortable temperature

2- The subject should be in complete physical and mental rest.

-The electric activity appears on a multi-channel recorder as waves of variable intensity (0-200 mV) and frequency (1-50 Hz).



Alpha

-8-13 Hz & 50 µv

-Regular & rhythmic

-Adult

-Parito-occipital region.

-Physical and mental rest

-Awake but with eyes closed

Alpha 

Beta

-18-30Hz & 20 µv

-Irregular & non-rhythmic

-Adult

-Frontal region

-Intense activation of the CNS i.e. during thinking and tension

Beta 

Theta

4-7 Hz & 100 µv

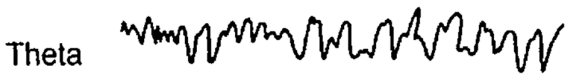
Regular and large

Partial & Temporal

In Children

& in adult during light

Sleep and may be in adults during emotional disappointment



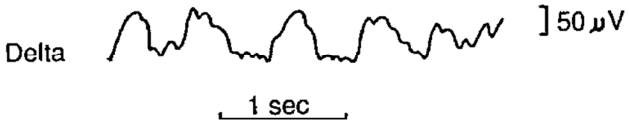
Delta

-1-3 Hz & 100 µv

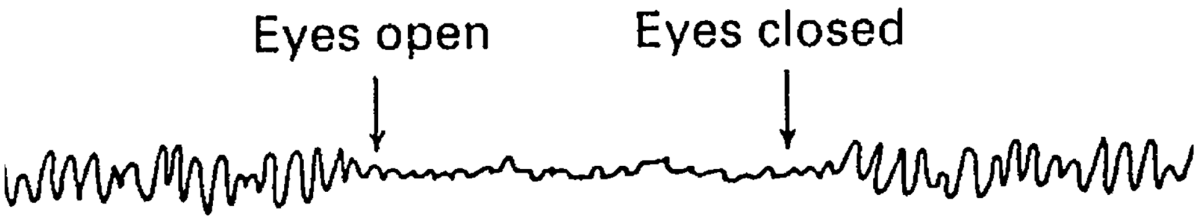
-Regular& high voltage

-Infants & in adults during deep sleep

coma, anasthtesia



Desynchronization :alpha block :
Alert or Arousal response :



While the eyes are closed, synchronous discharge of many cerebral neurons produces alpha waves, but when the eyes are opened, faster low voltage irregular beta waves are recorded. This is known as "alpha block". It has also been called "de-synchronization" because it represents breaking up of the synchronized neural activity necessary to produce regular waves.

Clinical Uses of the EEG

1-Localizing brain tumors

2. Diagnosis of epilepsy

3.Diagnosis of sleep disorders.

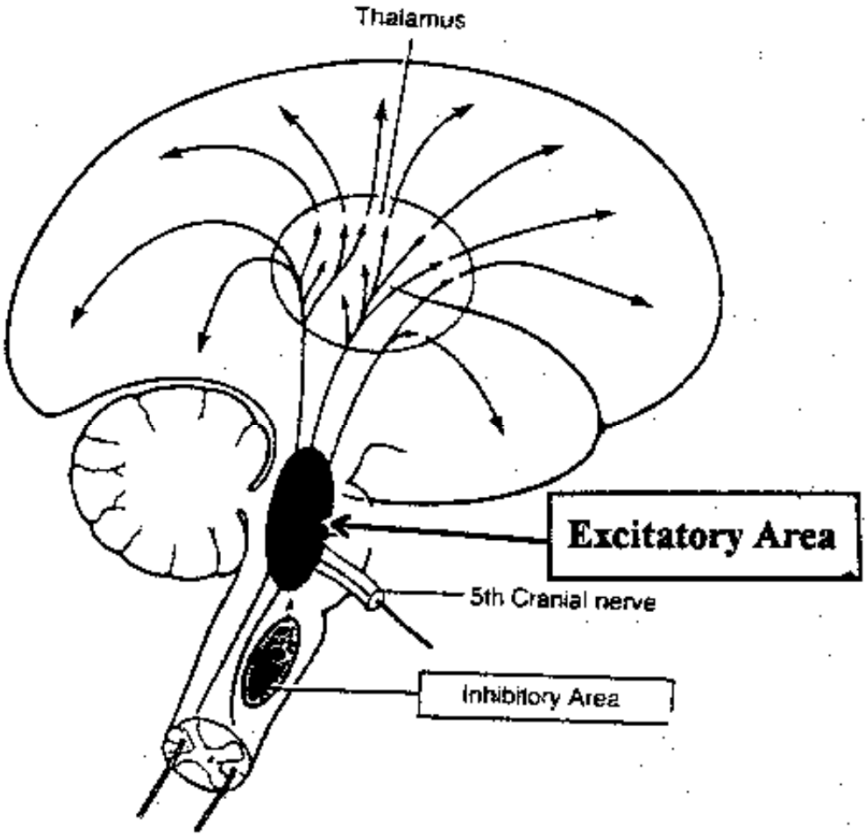
4.Confirmation of brain death (flat EEG).

Wakefulness And Sleep Cycle

sleep and **wakefulness**

= state-dependent behavior

Reflected by changes in cortical electrical activity: EEG changes



A. Factors that increase RAS activity:

1- The impulses from all the classical sensory pathways. Pain and proprioceptive stimuli are particularly effective and can arouse a person from sleep.

2- Descending impulses from the cerebral cortex have a strong excitatory effect on RAS. Emotions and voluntary movements help in keeping a person awake.

3-Epinephrine and norepinephrine secreted from the adrenal medulla produce alerting response.

B. Factors that decrease the RAS activity:

1- Impulses from the sleep-producing centers of the reticular formation.

2- Lesions that damage the brain stem cells e.g. vascular lesions, poisons, tumors and hypoxia.

3- Drugs e.g. barbiturates as they cause hyperpolarization of the neurons.

-Sleep is a state of loss of consciousness from which a person can be aroused by proper stimuli.

-As the person falls asleep, different stages can be identified from an EEG recording.

In mammals there are two sleep states:

- REM: rapid eye movement;
- NREM (non-REM)

Defined by:
• EEG
+ EOG, electroculography,
+ EMG, electromyography
(= polysomnography)

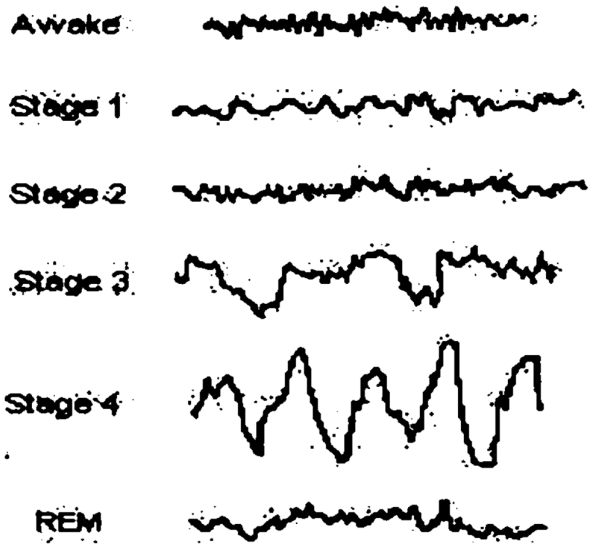
Most, if not all, living cells in plants and animals have rhythmic fluctuations in their function on a circadian cycle. Normally they become entrained, that is, synchronized to the day–night light cycle in the environment. If they are not entrained, they become progressively more out of phase with the light–dark cycle because they are longer or shorter than 24 h.

The entrainment process in most cases is dependent on the suprachiasmatic nuclei (SCN). These nuclei receive information about the light–dark cycle via a special neural pathway, the retinohypothalamic fibers. Efferent fibers from the SCN initiate neural and humoral signals that entrain a wide variety of well-known circadian rhythms including the sleep–wake cycle and the secretion of the pineal hormone melatonin.

Slow-wave sleep (Non-Rapid Eye Movement):

- **Stage 1&2&3&4**
- **<u>Character</u>**

Theta → Theta with Sleep spindles → Theta → delta waves→delta max



Non- REM

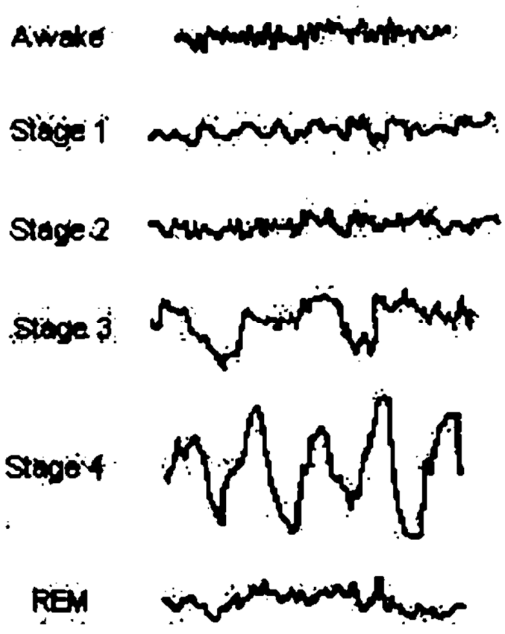
- Most of the sleep during the night occupies about 80% of sleep time.
- Eyes deviate up .
- Dreams are present, but are not remembered because they are not consolidated in the memory.
- Talking and walking are present
- HR&ABP&RR → decrease
- Ms Tone → Decreased

Rapid Eye Movement Sleep (REM sleep)

-Irregular low voltage, high frequency waves

-Resembles that seen in alert state (beta waves).

<u>REM sleep is also called paradoxical sleep.</u>



REM

-Occurs in episodes of 5-30 min, which recur about every 90 min of NREM sleep occupies

-20% of sleep duration.

-Rapid eye movement

-Dreams which are remembered

-Increase : → HR & ABP & RR

-Marked hypotonia

-Beta waves → Irregular fast, low waves

Distribution of sleep stages

- In a typical night of sleep, a young adult first enters NREM sleep, passes through stage 1 and 2 and spends 70-100 minutes in stages 3 and 4. Sleep them lightens and a REM period follows. This cycle is repeated at intervals of about 90 min throughout the night.

Mechanisms of sleep

(1) Passive mechanism i.e. as a result of its *fatigue* (after a period of wakefulness) or by *decreasing its activity* through elimination of its exciting stimuli e.g. the visual, auditory, painful and other stimuli.

(2) Active mechanism : This is *more accepted* as a mechanism of sleep.

Active mechanism of sleep:

Transitions between sleep and wakefulness manifest a circadian rhythm consisting of an average of 6–8 h of sleep and 16–18 h of wakefulness. Nuclei in both the brainstem and hypothalamus are critical for the transitions between these states of consciousness.

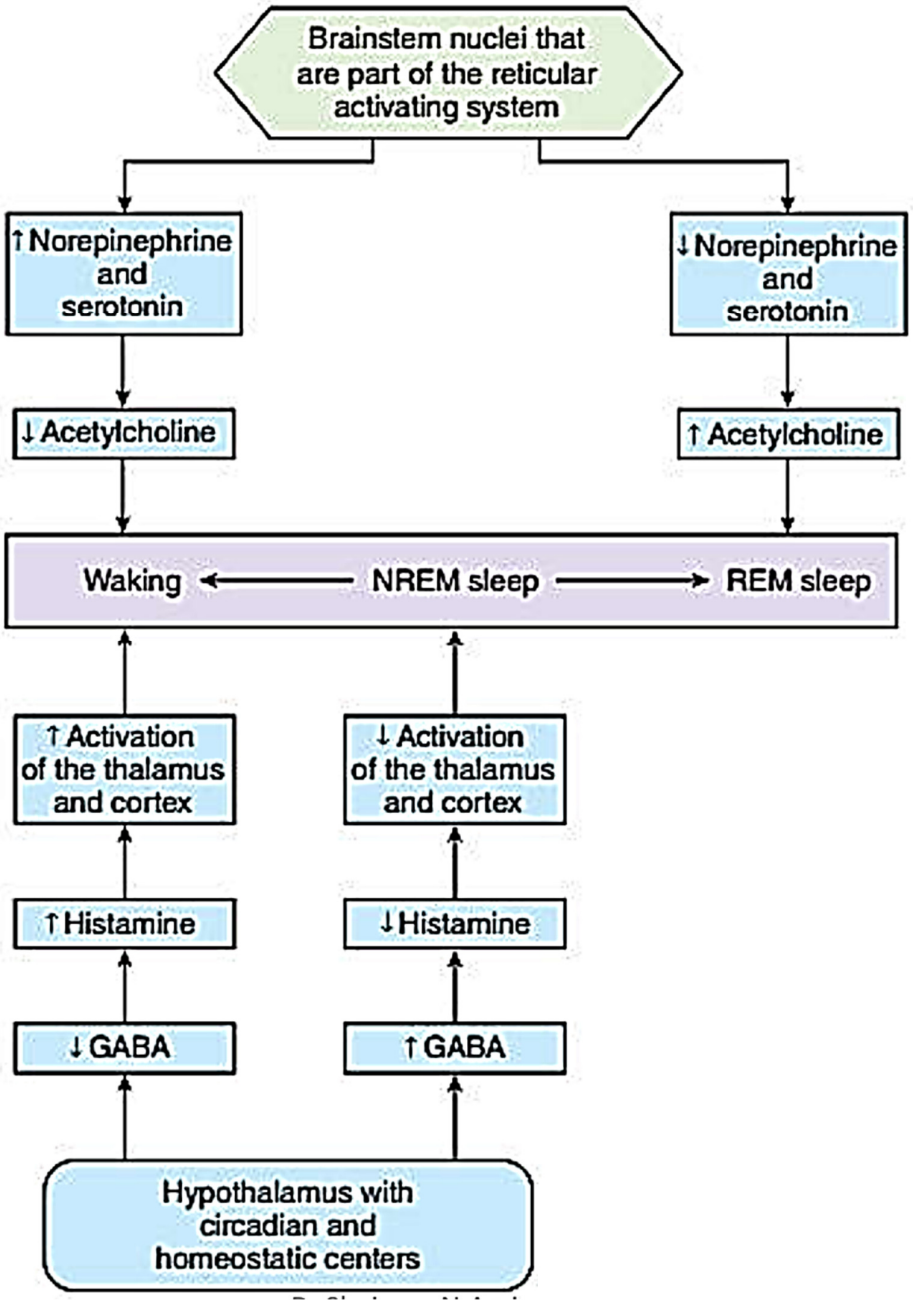
One theory regarding the basis for transitions from sleep to wakefulness involves alternating reciprocal activity of different groups of RAS neurons.

In this model, wakefulness and REM sleep are at opposite extremes. When the activity of norepinephrine- and serotonin-containing neurons is dominant, there is a reduced level of activity in acetylcholine-containing neurons in the pontine reticular formation.

This pattern of activity contributes to the appearance of the awake state. The reverse of this pattern leads to REM sleep.

When there is a more even balance in the activity of the aminergic and cholinergic neurons, NREM sleep occurs. In addition, an increased release of GABA and reduced release of histamine increase the likelihood of NREM sleep

The orexin released from hypothalamic neurons may regulate the changes in activity in these brainstem neurons.


Brainstem nuclei that are part of the reticular activating system
↑ Norepinephrine and serotonin
↓ Norepinephrine and serotonin
↓ Acetylcholine
↑ Acetylcholine
Waking
NREM sleep
REM sleep
↑ Activation of the thalamus and cortex
↓ Activation of the thalamus and cortex
↑ Histamine
↓ Histamine
↓ GABA
↑ GABA
Hypothalamus with circadian and homeostatic centers

Sleep disorders

1- Insomnia:

It is insufficient sleep that occurs in adults due to :

1- Psychological factors e.g. anxiety

2- Intake of analeptics e.g. coffee.

2- Somnambulism:

"*sleep walking*"

-More common in male children.

-The person walks with eyes opened, and avoid obstacle and when awakened can not remember what he did.

3- Narcolepsy:

Irresistible sleep during daytime activities which starts with sudden onset of REM sleep.

Narcolepsy has a familial incidence strongly associated with a class II antigen of the major histocompatibility complex on chromosome 6 at the HLA-DR2 or HLA-DQW1 locus, implying a genetic susceptibility to narcolepsy.

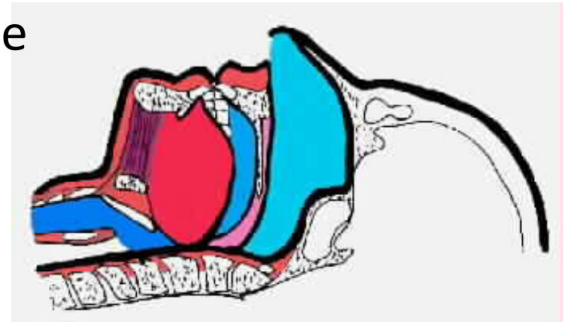
The HLA complexes are interrelated genes that regulate the immune system Compared to brains from healthy persons, the brains of persons with narcolepsy often contain fewer hypocretin (orexin)-producing neurons in the hypothalamus.

It is thought that the HLA complex may increase susceptibility to an immune attack on these neurons, leading to their degeneration.

4- Sleep apnea:

-Caused by obstruction of the airways during sleep.

-Effort to overcome the obstruction awakens the person from sleep.



Obstructive sleep apnea (OSA) is the most common cause of daytime sleepiness due to fragmented sleep at night and affects about 24% of middle-aged men and 9% of women in the United States. Breathing ceases for more than 10 s during frequent episodes of obstruction of the upper airway(especially the pharynx) due to reduction in muscle tone.

The apnea causes brief arousals from sleep in order to reestablish upper airway tone. An individual with OSA typically begins to snore soon after falling asleep. The snoring gets progressively louder until it is interrupted by an episode of apnea, which is then followed by a loud snort and gasp as the individual tries to breathe.

OSA is not associated with a reduction in total sleep time, but individuals with OSA experience a much greater time in stage 1 NREM sleep (from an average of 10% of total sleep to 30–50%) and a marked reduction in slow-wave sleep (stages 3 and 4 NREM sleep).

The pathophysiology of sleep apnea includes both a reduction in neuromuscular tone at the onset of sleep and a change in the central respiratory drive

5- REM behavior disorder:

- Hypotonia fails to occur.
- The patients with this condition act out their dreams, they even jump out of bed to do battle with imagined aggressors.

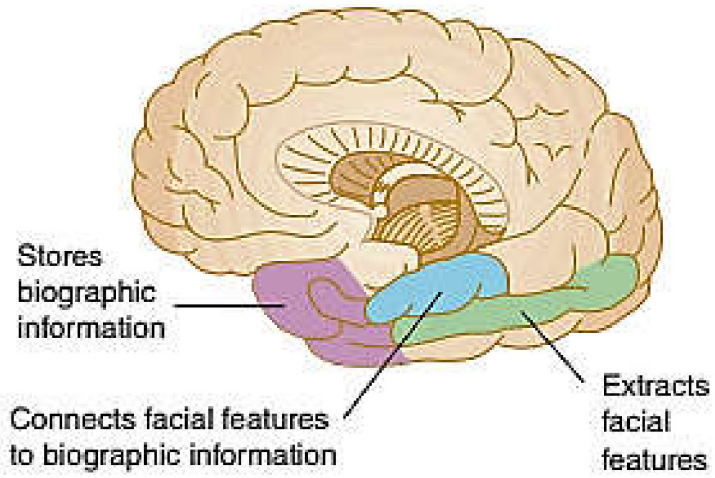
Disorders of association

- **Agnosia** – disorders of high-level sensory analysis. is the general term used for the inability to recognize objects by a particular sensory modality even though the sensory modality itself is intact.
- **Apraxia** – disorders of high-level motor coordination and appropriateness (Execution of skilled sequences)
- **Aphasia** – disorders in communicating and using symbols.

RECOGNITION OF FACES

An important part of the visual input goes to the inferior temporal lobe, where representations of objects, particularly faces, are stored Faces are particularly important in distinguishing friends from foes and the emotional state of those seen.

In humans, storage and recognition of faces is more strongly represented in the right inferior temporal lobe in right-handed individuals, though the lef lobe is also active



- **Prosopagnosia** (='face blindness') refers to a severe deficit in recognizing familiar people from their face.

left–right asymmetry in the brain

Human language functions depend more on one cerebral hemisphere than on the other. Tis hemisphere is concerned with categorization and symbolization and has often been called the dominant hemisphere. However, the other hemisphere is not simply less developed or “nondominant;” instead, it is specialized in the area of spatiotemporal relations, the identifcation of objects by their form and the recognition of musical themes and recognition of faces. Consequently, the concept of “cerebral dominance” has been replaced by a concept of **complementary specialization** of the hemispheres, one for sequential-analytic processes **(the categorical hemisphere)** and one for visuospatial relations (**the representational hemisphere).**

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****Good Luck****