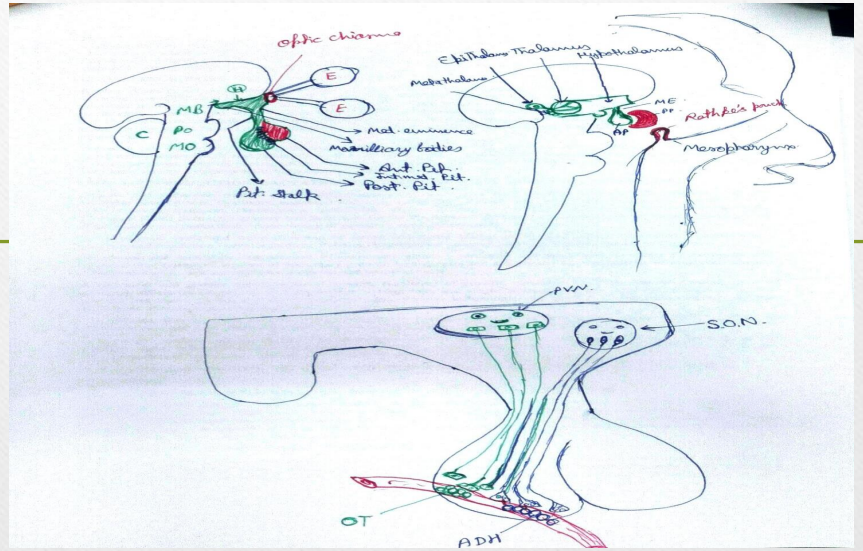
Nervous and Muscular Systems



Nervous System

- **Organization of nervous system- Mechanism of information processing, hierarchical control. Major function system- sensory, consciousness, emotion, motor and visceral control.**
- **Basic functional unit - neuron structure, type- functional characteristics of sub-units of neuron. Membrane potential - ionic basis of resting membrane potential (RMP) nerve action potential, excitation and propagation of impulse characteristics- latent period- refractive-ness, threshold level-all and none characteristics.**
- **Degeneration and regeneration of nerve fibre. Synaptic and junctional transmission.**
- **Functions of nervous system-reflexes-control of posture and movements, autonomic nervous system and visceral control. Neurotransmitter wakefulness, sleep cycle.**
- **Higher function of neurons system - learning, memory, electroencephalography.**
- **Sense organs and receptors physiology of special senses –**
- **Eye: functional morphology, nourishment and protection neural pathway, receptors- optics, ocular muscles and movements, photochemistry, Vision defects**
- Ear: Physiology of hearing and common hearing impairment. Vestibule apparatus. Physiology of olfaction and taste

Course content

- Muscle Physiology-basic muscle unit characteristic-electrical phenomenon in muscle cell - muscle action potential
- Excitation and propagation of impulse characteristics- latent period refractive ness, threshold level-all and none characteristics.
- Contractile mechanism - excitation - contraction coupling-neuro-muscular transmission
- Types of muscle contraction, phenomenon of fatigue, rigor mortis.

Organization of Nervous System

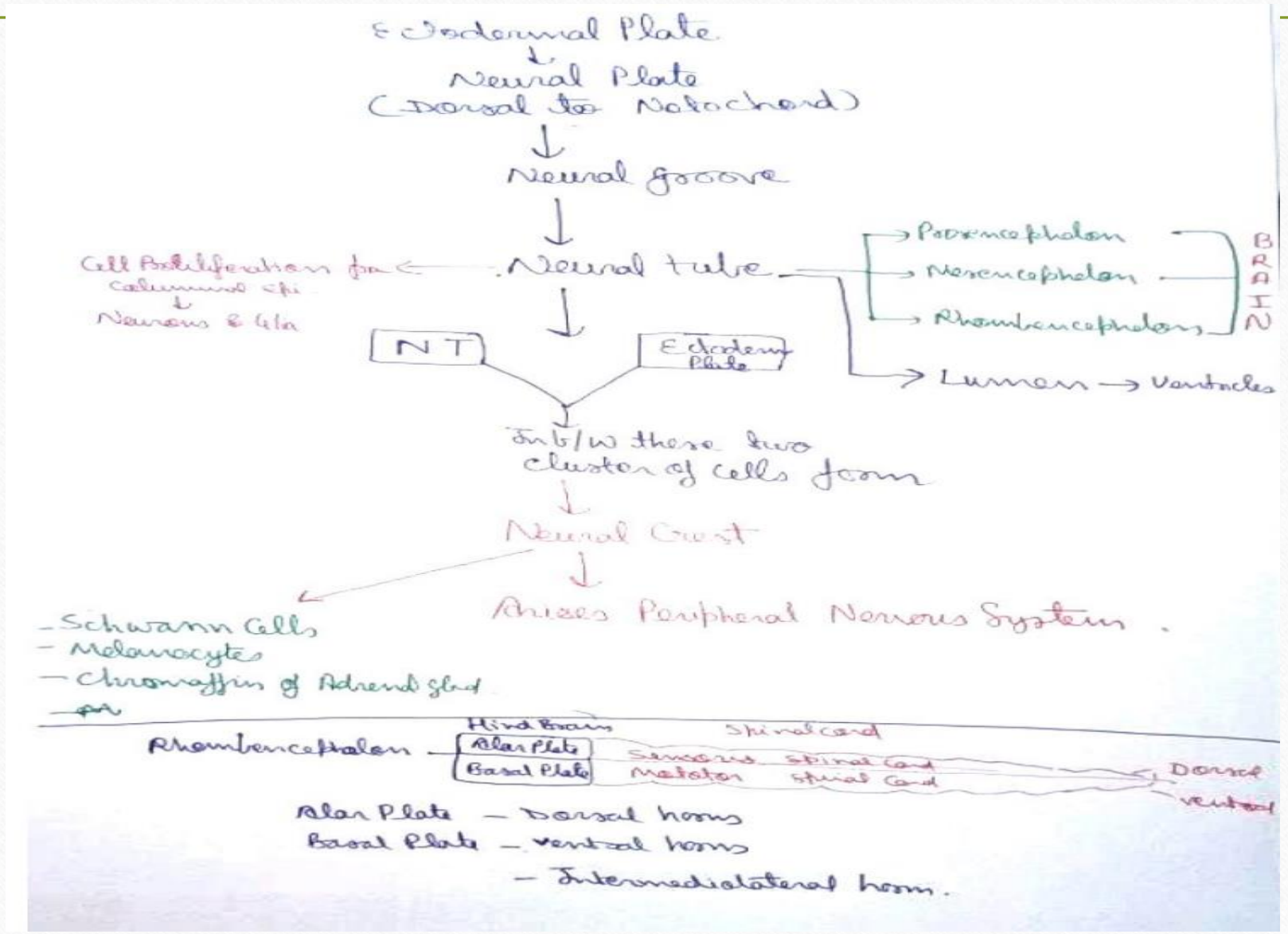
Mechanism of information processing

Hierarchial control

Introduction

- The different body cells function in an integrated manner for which communication between the various cells is highly essential. Communication between cells is provided by two systems in the body
- (**1) Nervous system (2) Endocrine system.**

- The nervous system can be subdivided into two major divisions
  - **Central nervous system (CNS)**
  - **Peripheral nervous system (PNS)**


Ectodermal Plate
Neural Plate
(Dorsal to Notochord)
Neural groove
Neural tube
Cell Proliferation for
Columnar cell
Neurons & Glia
Prosencephalon
Mesencephalon
Rhombencephalon
BRAIN
Lumen → Ventricles
NT
Ectoderm Plate
In b/w these two
cluster of cells form
Neural Crest
Arises Peripheral Nervous System.
- Schwann Cells
- Melanocytes
- Chromaffin of Adrenal Gland
Rhombencephalon
Hind Brain
Spinal cord
Alar Plate
Basal Plate
Sensory Spinal Cord
Motor Spinal Cord
Dorsal
Ventral
Alar Plate – Dorsal horns
Basal Plate – Ventral horns
– Intermediolateral horn.

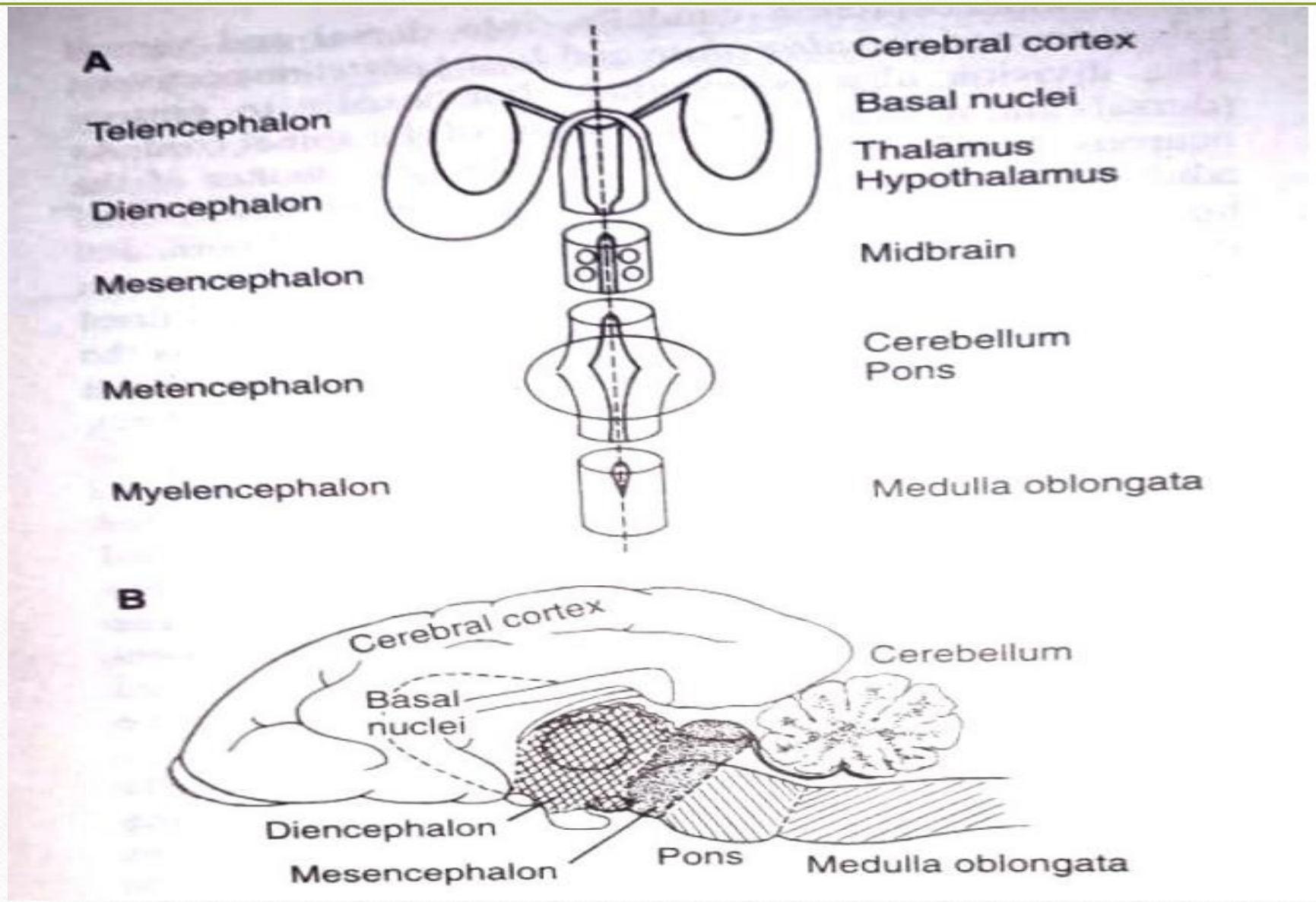

A
Telencephalon
Diencephalon
Mesencephalon
Metencephalon
Myelencephalon
Cerebral cortex
Basal nuclei
Thalamus
Hypothalamus
Midbrain
Cerebellum
Pons
Medulla oblongata
B
Cerebral cortex
Basal nuclei
Cerebellum
Diencephalon
Mesencephalon
Pons
Medulla oblongata

Table 42.1. Derivatives of the neural tube

Primary division	Subdivisions	Lumen	Major derivatives	Cranial nerves
Prosencephalon	Telencephalon	Lateral ventricles	Cerebral cortex	I
			Basal nuclei	
	Diencephalon	Third ventricle	Pineal	II
			Thalamus	
			Hypothalamus	
Mesencephalon	Mesencephalon	Mesencephalic aqueduct	Tectum	III, IV
			Tegmentum	
Rhombencephalon	Metencephalon	Fourth ventricle	Pons	V
			Cerebellum	
	Myelencephalon	Fourth ventricle	Medulla oblongata	VI, VII, VIII, IX, X, XI, XII
Spinal cord	Spinal cord	Spinal canal	Cervical	
			Thoracic	
			Lumbar	
			Sacral	
			Coccygeal	

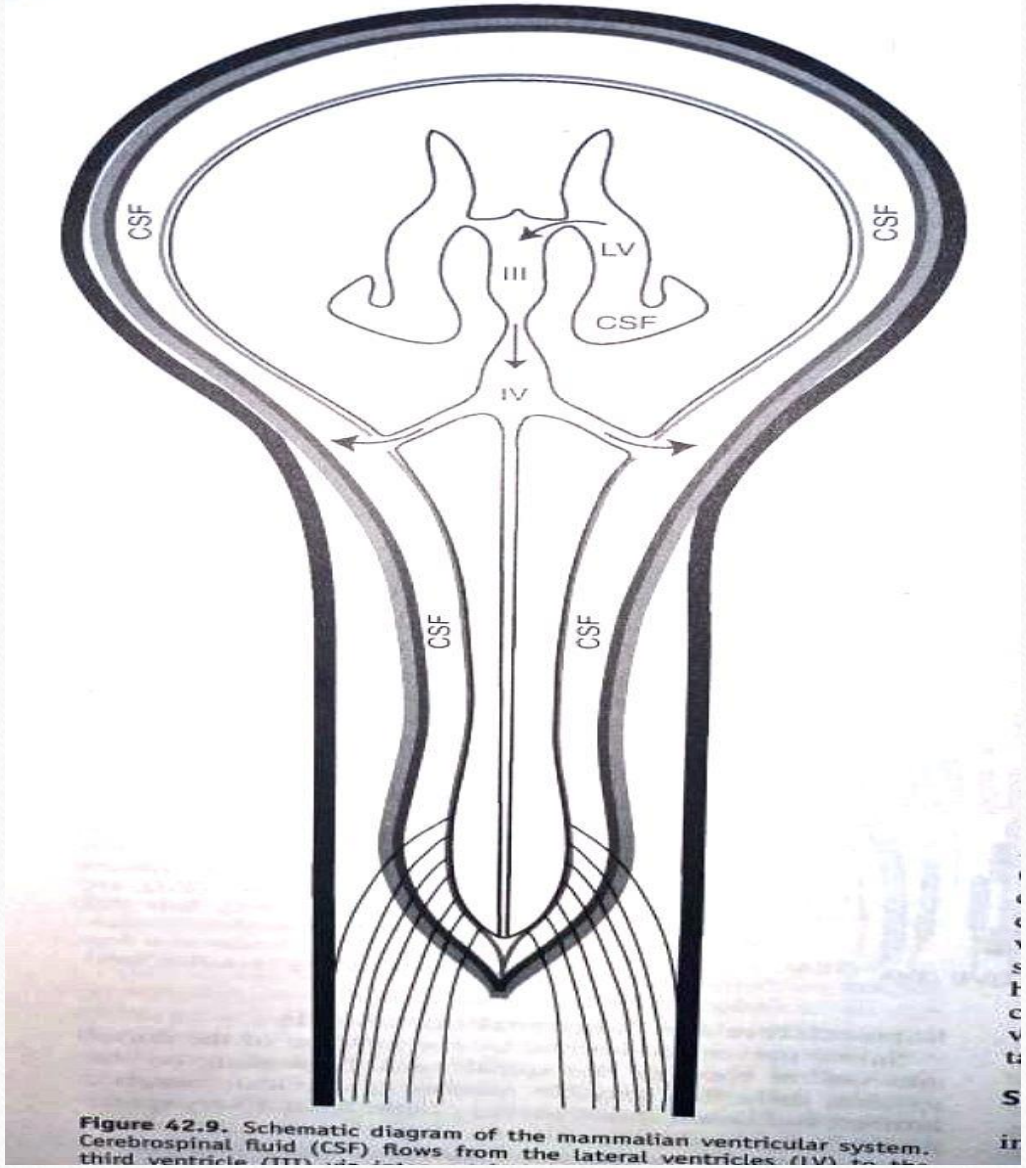
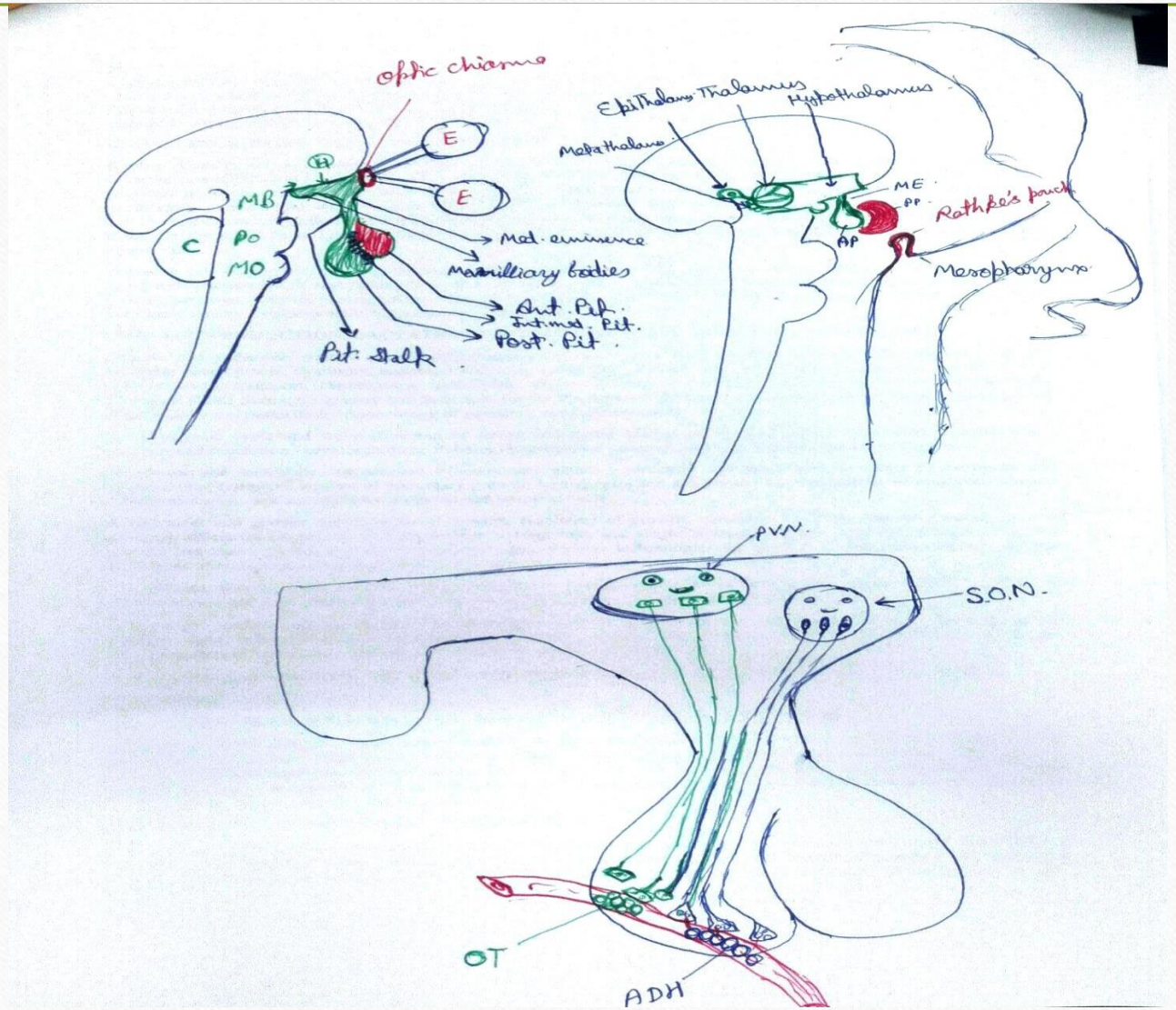


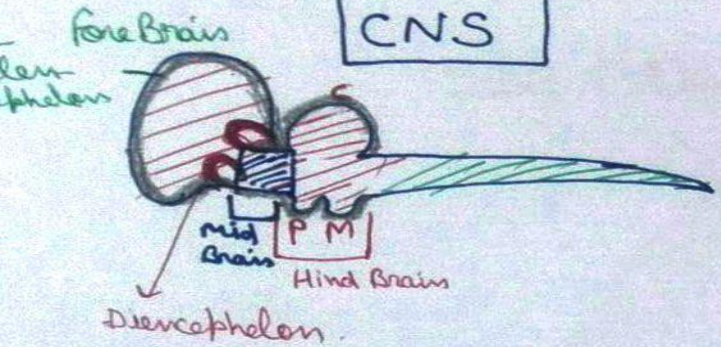
Figure 42.9. Schematic diagram of the mammalian ventricular system. Cerebrospinal fluid (CSF) flows from the lateral ventricles (LV) to the third ventricle (III)


optic chiasma
E
E
H
MB
C
Po
MO
Mat. eminence
Mamillary bodies
Ant. Pit.
Int.med. Pit.
Post. Pit.
Pit. stalk
Epithalamus
Thalamus
Hypothalamus
Metathalamus
ME
PP
AP
Rathke's pouch
Mesopharynx
PVN.
S.O.N.
OT
ADH

Nervous System

CNS

PNS



Sensory PNS

Motor PNS

Special Sensory

- Eyes
- Ear
- Tongue

General Sensory

Somatic Sensory

- Skin
- Locomotion
- S/C Tissue.

Visceral Sensory

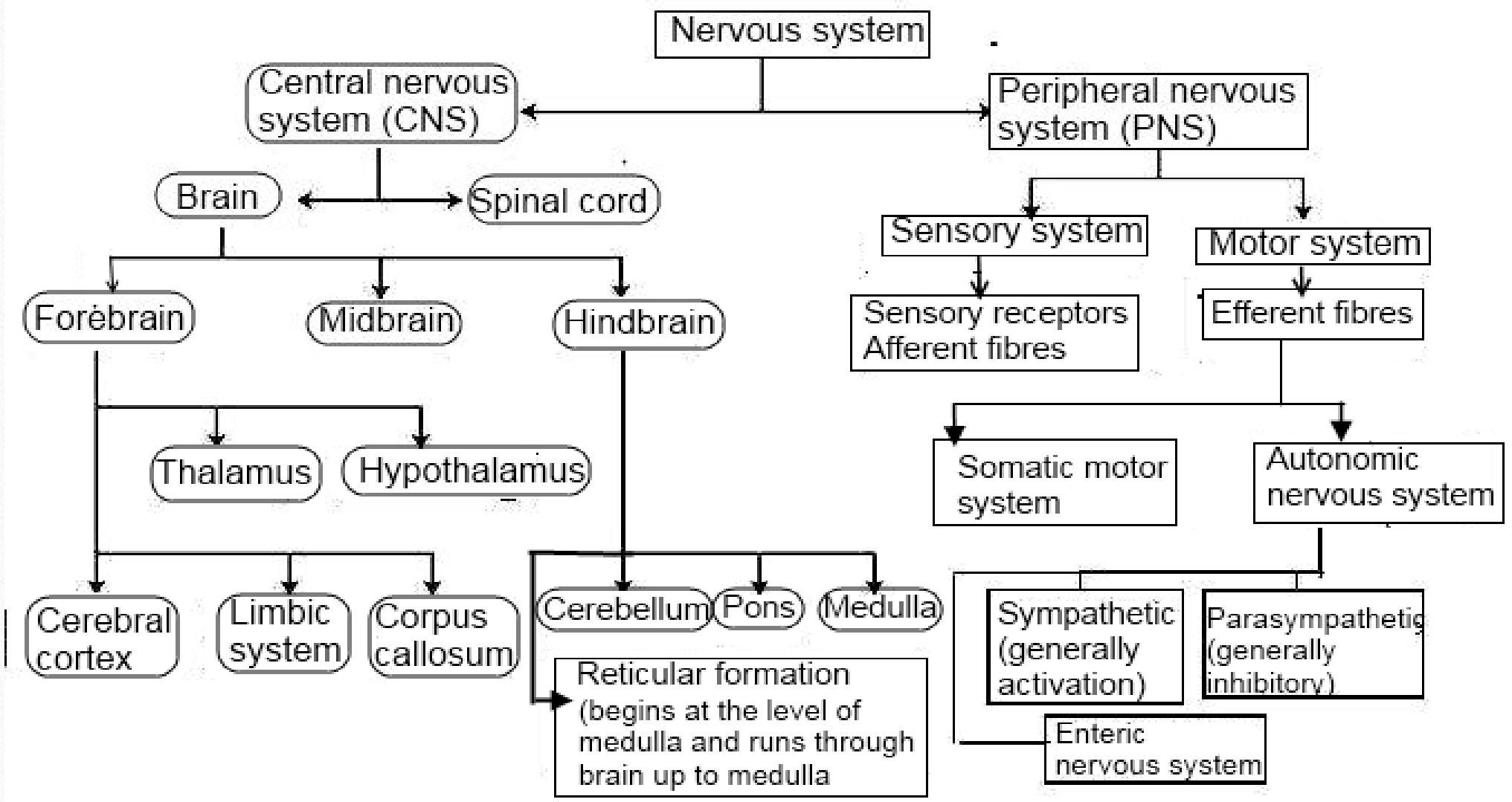
- Gut
- Liver
- Heart

Somatic Motor Response

Autonomic Motor Response

- Symp. NS
- Parasymp. NS

Hierarchy of Nervous System.


Nervous system
Central nervous system (CNS)
Peripheral nervous system (PNS)
Brain
Spinal cord
Sensory system
Motor system
Forebrain
Midbrain
Hindbrain
Sensory receptors
Afferent fibres
Efferent fibres
Thalamus
Hypothalamus
Somatic motor system
Autonomic nervous system
Cerebral cortex
Limbic system
Corpus callosum
Cerebellum
Pons
Medulla
Sympathetic (generally activation)
Parasympathetic (generally inhibitory)
Reticular formation
(begins at the level of medulla and runs through brain up to medulla
Enteric nervous system

Central Nervous System

- The CNS includes the brain and the spinal cord.
- The functions of the nervous system are carried out by ***neurons*** **and** ***glialcells***. The brain contains about 100 billion neurons and 10 times more glial cells.
- Neuron is the functional and structural unit of the nervous system; it consists of a *cell body* or soma located within the CNS and two elongated processes called the ***dendrites*** **and an** ***axon***.

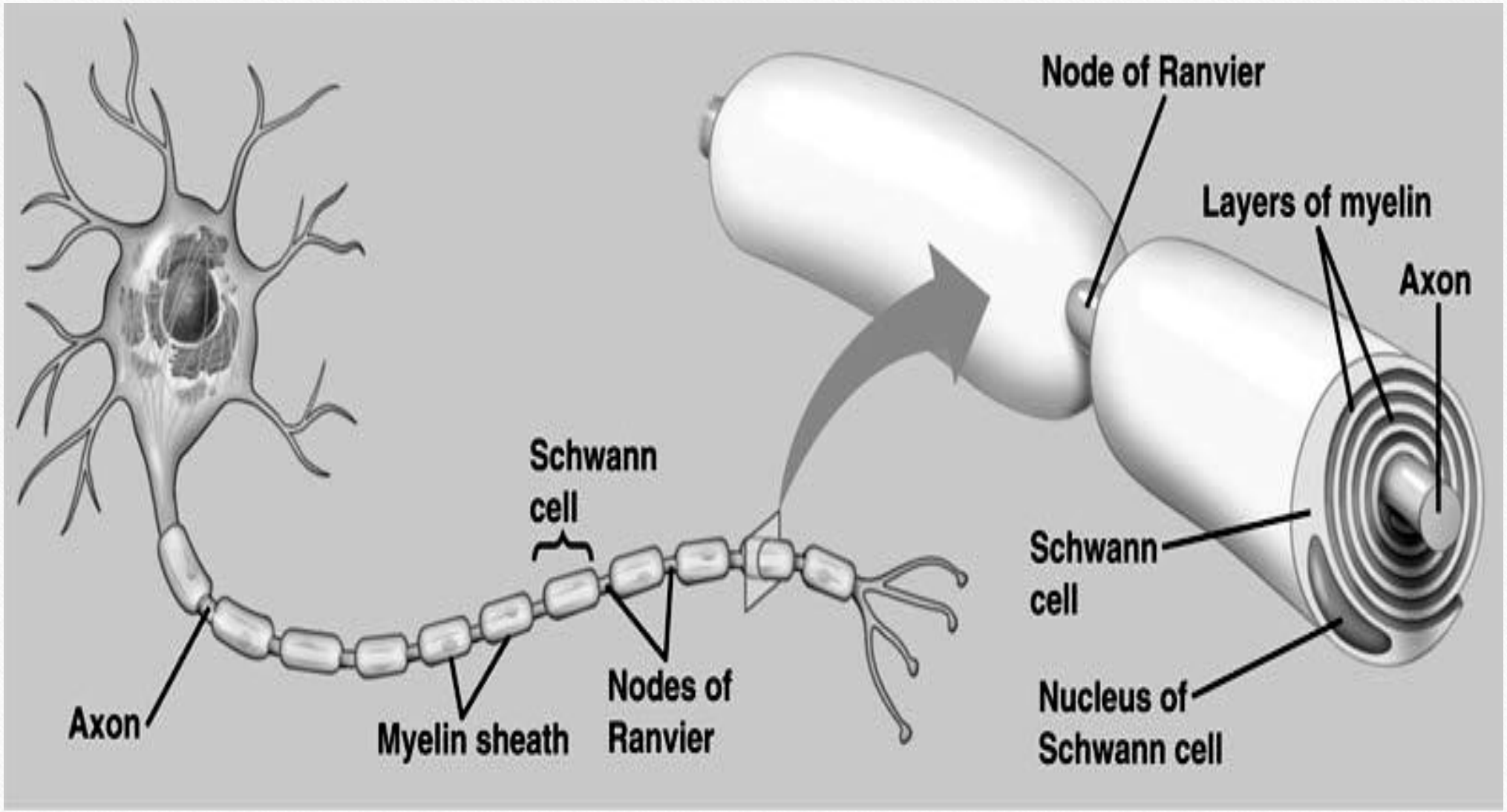
Peripheral Nervous System

The PNS consists of paired nerves extending from the spinal cord (spinal nerves) and the brainstem (cranial nerves) and it provides an interface between the CNS and the internal conditions of the body and external environment.
It includes a ***sensory system*** **and motor system**.

- **Sensory system** is formed by sensory receptors and afferent neurons that transmits information to the CNS. Motor system is further divided into somatic motor *and autonomic motor system* that controls skeletal muscles (voluntary motor activity).
- ***Autonomic system*** that controls involuntary (*visceral*) activities like regulating glands, smooth muscles, heart etc.
- The autonomic system is divided into sympathetic, parasympathetic and enteric nervous systems.

Nerve Cells (Neurones)

- **Nerve cells can be classified according to the number and arrangement of their processes**
  - **Pseudounipolar cells** – have a single process from the cell body that divide into a central and peripheral branches e.g. dorsal root ganglion cells
  - **Bipolar cells**–have two processes - one axon and one dendrite. e.g. sensory cells in retina and olfactory system
  - **Multipolar cells** – have numerous branching dendrites and one axon. E.g. motor neurons in the ventral gray column of spinal cord.
- Based on function, nerve cells can be divided into
- **Sensory (afferent) neurons** that carry impulses to the CNS
- **Motor (efferent) neurons** that conduct impulses from the CNS to effector organs


Node of Ranvier
Layers of myelin
Axon
Schwann cell
Schwann cell
Nodes of Ranvier
Axon
Myelin sheath
Nucleus of Schwann cell

Nerve Cell body (Soma):

- Cell body or soma of a neuron consists of a nucleus and cytoplasm (neuroplasm) and organelles like mitochondria (for energy), Golgi network, microsomes, ribosomes and the endoplasmic reticulum (for biochemical synthesis).
- *Mature neurons do not divide*.
- In addition to these organelles, the neuroplasm also has *Nissel granules* (tigroid bodies) which are chromatid substances placed on the rough endoplasmic reticulum; it is concerned with protein synthesis.

The cell membrane of the soma extends as dendrites.

Dendrites:

- The dendrites are characterised by repeated branching arising from soma
- They function as the receptive sites for the impulses into the neurons. Nerve endings from other neurons terminate either on the soma or dendrite
- As a general rule, the dendrites convey impulses towards the soma.
- In cerebral and cerebellar cortex, the dendrites have small projections called *dendritic spines* which help to increase the surface area.

Axon:

Axon is the extension of the cytoplasm of the soma and is enclosed in cell membrane that forms the nerve fibre.

The cytoplasmic portion of the axon is referred to as "**axoplasm**".

The axon originates from a thickened area of the cell body called **axon hillock.**

The axon may give off collateral branches along their course.

Axons terminate in branches with each branch ending in **synaptic knobs or terminal boutons.**

In general, the axons convey or discharge impulses away from the soma to other neurons.

The nerve cells are secretary cells and the secretary zone is the axon terminal where **small molecule neurotransmitters** are synthesised and stored.

- Protein synthesis occurs in the cell body (due to the presence of nucleus) and proteins and polypeptides are transported to the axon terminal along the neurofibrils and neurotubules by **axoplasmic flow or axoplasmic transport**. Both antrograde and retrograde transport occurs along the axon.
- The **neurofibrils** are the delicate thread like structures that travel from the terminal ends of dendrites to the terminal end of the axon which form a net work in the soma.
- **One nerve cell can communicate with 100,000 neurons.**
- **Large diameter causes more velocity of conduction and diameter could be 20 micro meter to one tenth of micrometer.**

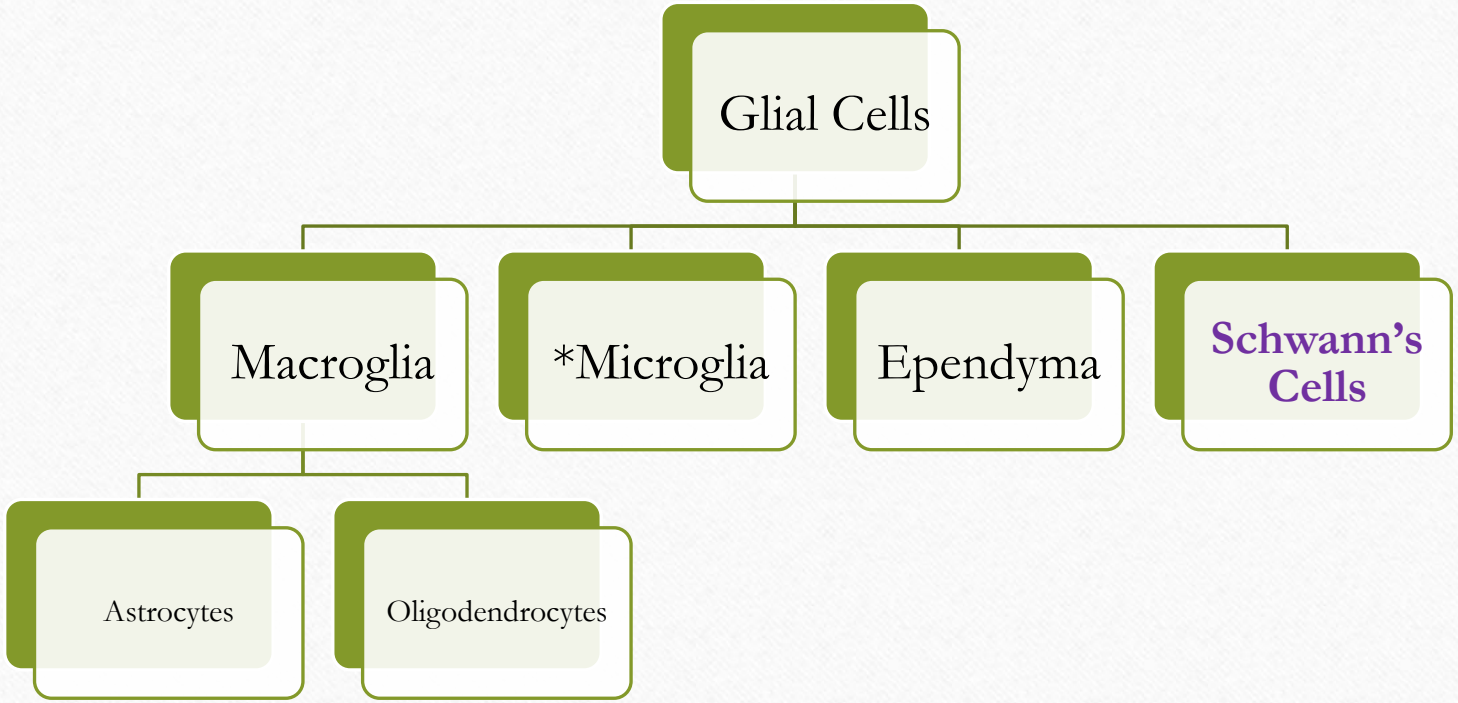
MYELINATED FIBRES

•The Schwann cell membrane is rich in sphingomyelin (a phospholipid) that forms a sheath around an axon which is referred to as *myelin sheath*.
•Myelin forms when a Schwann cell wraps its membrane around an axon up to 100 times.
•At the junction between two successive Schwann cells along the axon is present a small uninsulated area of the axon membrane which is known as "**Node of Ranvier**".
•These nodes aid ionic flow between the extracellular and intracellular fluid of the axon.
•Myelin sheath acts as an excellent insulator and capacitor by preventing the flow of ions through the membrane and thereby temporarily stores the electricity as much as fifty folds.

Glial Cells

- **GLIAL CELLS (Neuroglia or interstitial cells):**
- They are the supporting cells of nervous system.
- The glial cells are ten times more in number than the neurons.
- **Glial cells are involved in buffering of K ions and Ca ions.**
- **These provide pathways for migration of neurons during development and also during regeneration**
- **These secrete cytokines in disease**
- **These are involved in neurotransmitter reuptake.**
- **These are also involved in CSF production.**
-

Glial Cells


Glial Cells
Macroglia
*Microglia
Ependyma
Schwann's Cells
Astrocytes
Oligodendrocytes

Glial Cells

There are four major kinds of glial cells

- **Astrocytes*:*** They have extensive branching, found closely attached to the blood vessels of the brain and spinal cord and contribute to the **"*blood brain barrier*".**
- **Gliosis: During Injury Astrocytes tend to enlarge and proliferate this process is known as gliosis**
- **Oligodendrocytes*:*** They are often found in columns around the neurons of CNS and are similar to the Schwann cells of the peripheral nerves.
- They are the myelin forming cells in the CNS. Each cell can form the myelin sheath around many axons.
- Eg. Multiple Sclerosis is a well known demyelinating disease.

- Astroglia and oligodendroglia together are called as ***macroglia*.**

- **Microglia:** They are the smallest of glial cells and have amoeboid movement and phagocytic in function.

- **Schwann's cell:** They produce the connective tissue structure, the *myelin sheath* – a protein-lipid complex that is wrapped. around the axon and it is an electrically insulating coat present around the axon fibres of the peripheral nerves

CNS

- A cluster or group of nerve cell bodies found in brain and spinal cord are called as ***nuclei*** and those lying out of the brain and spinal cord are referred to as ***ganglia***.

- The term **nerve / nerve fibre** denotes a group of axon processes of many neurons and enclosed in a connective tissue and located in the PNS.

- In the CNS, the group of axons running parallel is termed as ***tract*** **and** ***fasciculus*****.**

NS

CNS

PNS

Tracts
(Apons).

Grey Matter
(cell body)

White Matter
(Axons)

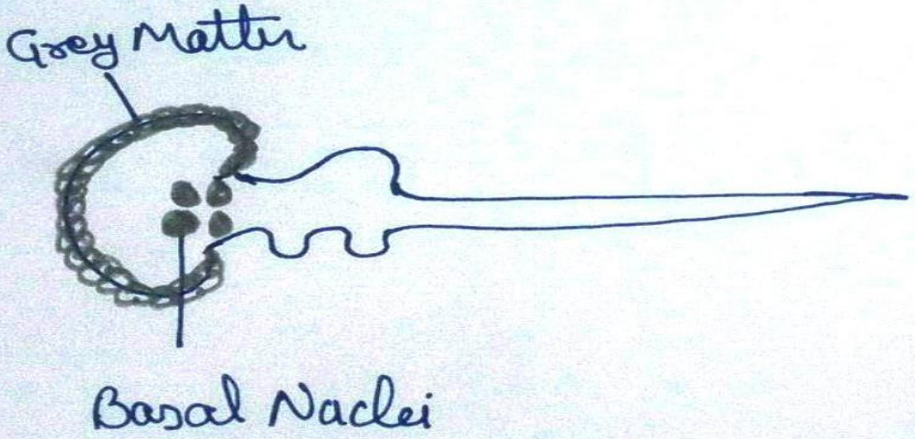
Cortex

Nuclei

Ascending
&
Descending
Tracts

Commisure
fibres

Association
fibres.



- Grey matter: The groups of cell bodies peripheral to nervous system is called cortex.
- White matter: The groups of axons placed centrally in brain is called **white matter** while the groups of those axons in spinal cord are called **tracts**.
- If these tracts are made up of sensory nerves from down towards brain then these are called as **ascending tracts**, If these tracts are made up of motor neurons from brain towards body parts then these are called as **descending tract.**

Reticular formation

- Reticular formation: Deep part of the brain stem where sensory and motor tracts decussate and there is mix up of grey and white matter is called Reticular Formation.

DEGENERATION AND REGENERATION IN NERVOUS TISSUE

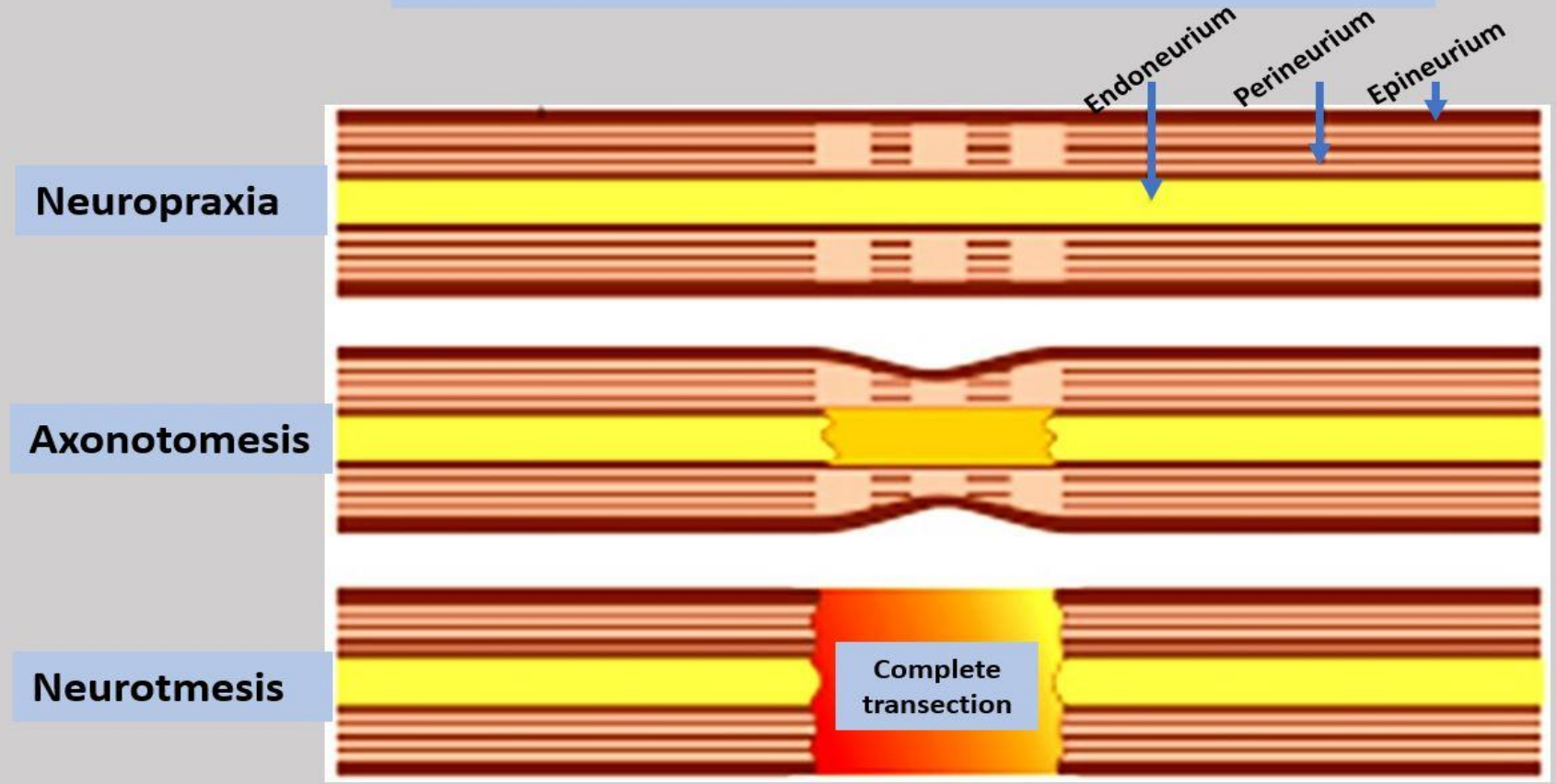
- The number of neurons in the body is fixed at the time of birth, after which if a neuron is destroyed it cannot be replaced.
- Under certain circumstances, a degenerated peripheral nerve fibre may be that constitute degeneration in nerve cells and their processes replaced, which can occur only if the nerve cell body remains intact
- The cell body if destroyed cannot be replaced.
- The changes may be initiated by transection, crushing of the nerve fibre, by toxins or by interfering with blood supply.

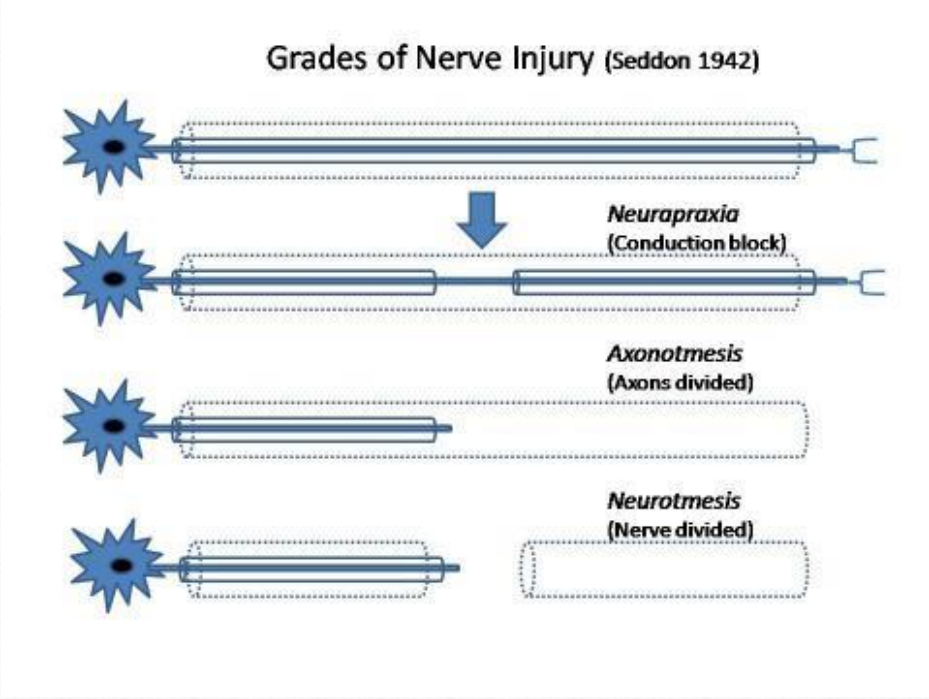
Causes of nerve injury

- Toxins
- Crushing of nerve fibres
- Transection of nerve fibre
- Obstruction blood flow

- (1) **Contusions (neuropraxic)**
- **(2) Crush (axonotmesis)**
- **(3) Transection (neurotmesis)**

SEDDON'S CLASSIFICATION OF NERVE INJURIES




Grades of Nerve Injury (Seddon 1942)
Neurapraxia
(Conduction block)
Axonotmesis
(Axons divided)
Neurotmesis
(Nerve divided)

Wallerian degeneration

- **Wallerian degeneration** is an active process of degeneration that results when a nerve fiber is cut or crushed and the part of the axon distal to the injury (i.e. farther from the neuron's cell body) degenerates. A related process of dying back or retrograde degeneration known as 'Wallerian-like degeneration' occurs in many neurodegenerative diseases.
- Eg. Alzheimer's disease

Changes in Peripheral Nerve Fibre

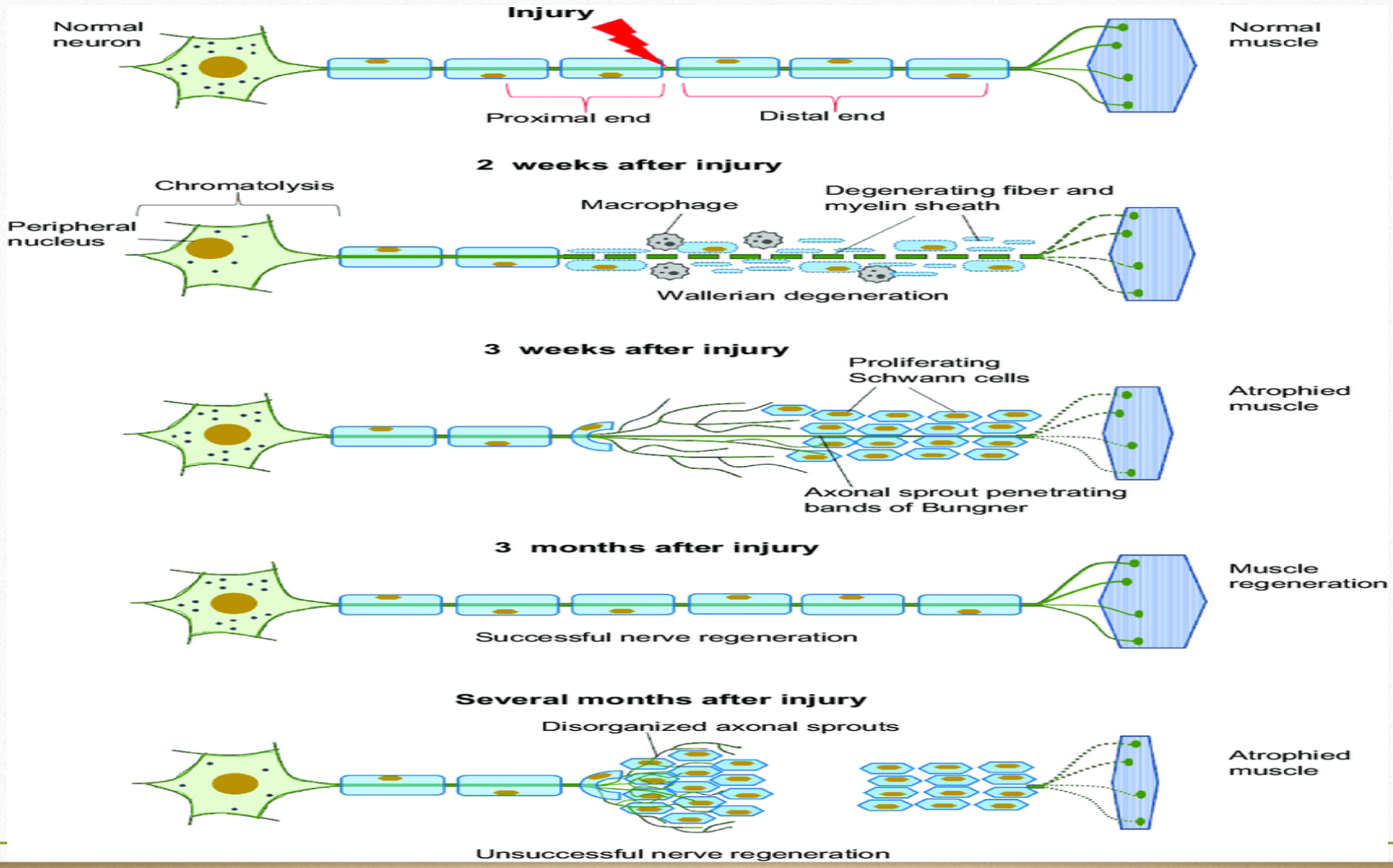
•Cell repair may occur even if the axon does not regenerate.
•In the CNS, most of the affected cells atrophy (because of abortive regeneration).
•In the peripheral neurons, if the peripheral axon is cut, changes described above occur but if the central axon is cut, changes in the ganglion cells are very slight
•When a nerve is cut, the peripheral portion (not attached with cell body) alters in appearance and in 3 to 4 days time loses its ability to conduct nerve impulses; the central portion (attached with cell body) may not undergo much change and can conduct impulses.

•The nerve sectioning leads to greater degenerative changes taking place in the peripheral part of the fibre called as **Wallerian degeneration.**

•After 30 days, all that is left of the nerve fibre is syncytial neurilemma known as *protoplasmic* or *band fibre (endoneurial tube)*.

•If conditions are favourable, complete regeneration may occur in the degenerated nerve fibre. This is effected by the nerve cell body.

- The portion of the axon connected with the cell body sends out a process (fibril) along the protoplasmic fibre, which finally reaches the termination of the old nerve fibre.
- This outgrowth becomes the axon of the regenerated nerve fibre. The protoplasmic fibre serves as a guide to the new axon up to its termination.
- The time required for regeneration of the nerve fibre varies with the distance between the cut ends. If the ends are brought close together, regeneration is relatively quick; if they are widely separated, regeneration may take years or may not occur at all.
- If regeneration does not take place, the nerve cell body and its attached axon undergoes degeneration.
- The rate of regeneration is about **2.5mm daily; may range 3 to 4mm/ day.**


Normal neuron
Injury
Normal muscle
Proximal end
Distal end
2 weeks after injury
Chromatolysis
Peripheral nucleus
Macrophage
Degenerating fiber and myelin sheath
Wallerian degeneration
3 weeks after injury
Proliferating Schwann cells
Atrophied muscle
Axonal sprout penetrating bands of Bungner
3 months after injury
Muscle regeneration
Successful nerve regeneration
Several months after injury
Disorganized axonal sprouts
Atrophied muscle
Unsuccessful nerve regeneration

Nerve Stimulation

- The membrane potential (Vm) or resting potential in a neuron which is not generating or conducting electrical signals is about -70 mV which is closer to the equilibration potential of K+.
- When a nerve cell is stimulated with a threshold intensity of stimulus, it will produce an action potential.
- A slowly rising current of stimulation fails to evoke an action potential in a neuron because the nerve cell adapts to the stimulus and this property is called **accommodation.**
- The action potential of the nerve cell obeys all-or-none law.
- Nerve cells have a low threshold for excitation.
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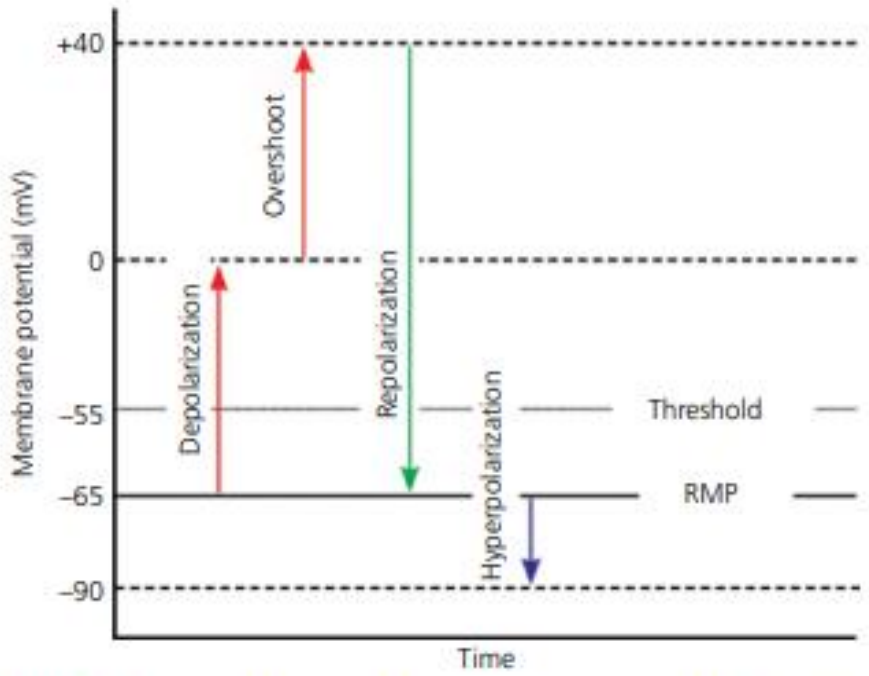
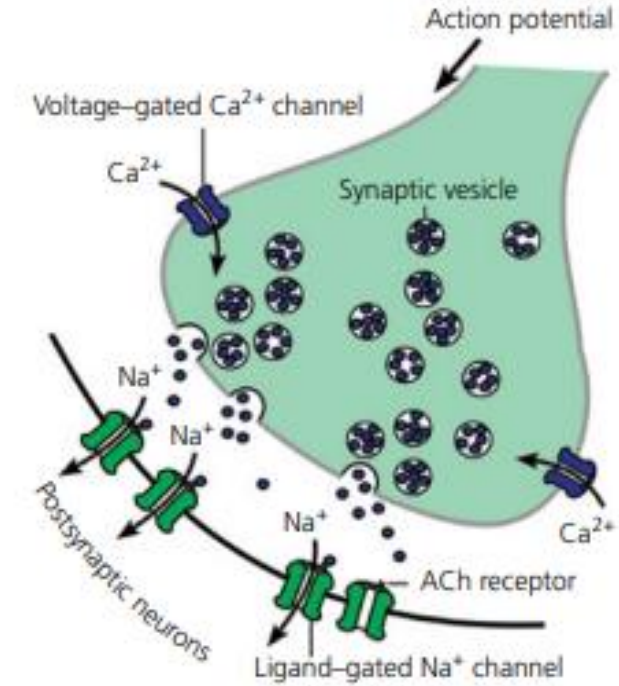
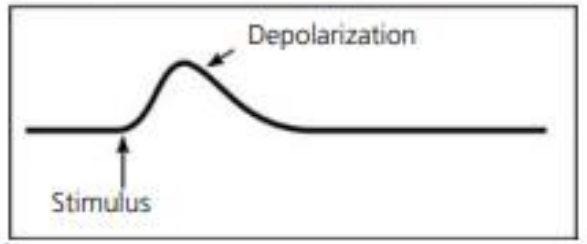






(A)

Figure 2.2 Terminology related to membrane potential of neurons. *Depolarization*: decrease in the potential difference across the plasma membrane, going to more positive. *Overshoot*: a portion of depolarization that causes the inside of the cell to be positively charged with respect to the outside. *Repolarization*: change in potential that returns the membrane potential to a negative value after the depolarization phase of an action potential. Repolarization returns the membrane potential to the resting membrane potential (RMP) (–65 mV). *Hyperpolarization*: increase in the potential difference across the

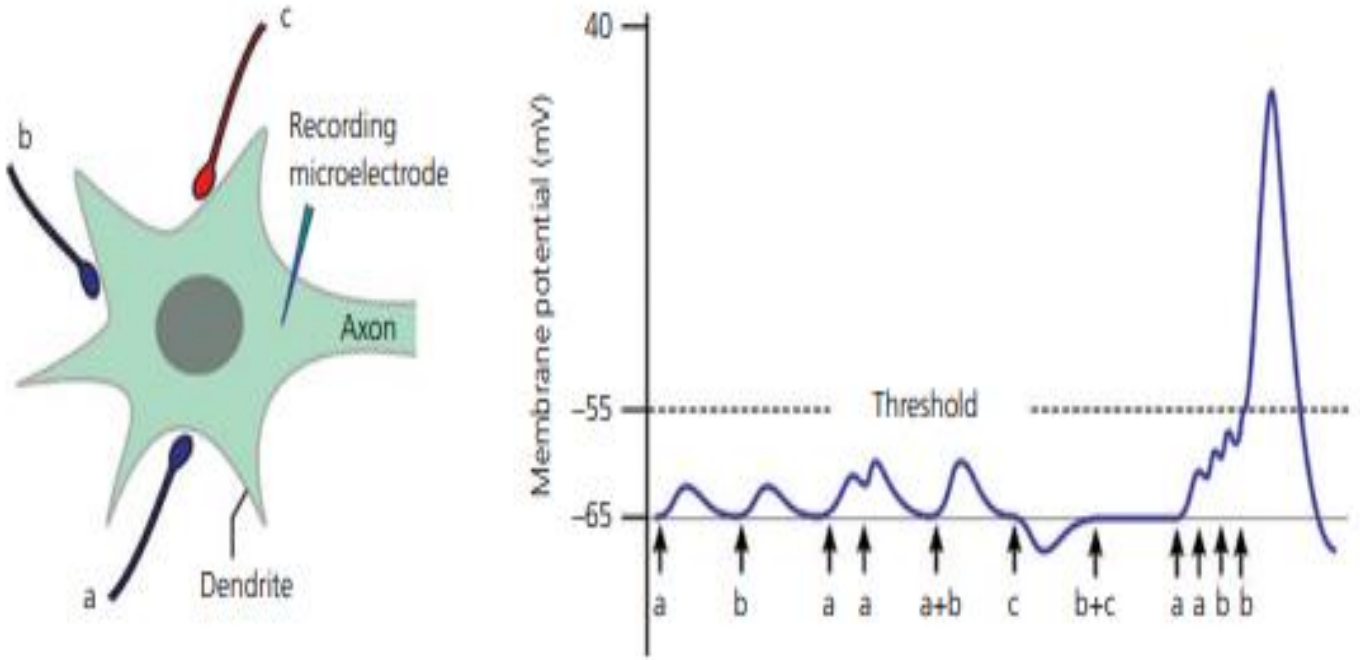


Figure 2.4 Summation of EPSPs and IPSPs at the postsynaptic neuron. Three presynaptic neurons (a, b, c) were stimulated at times indicated by the arrows on the graph, and the membrane potential was recorded in the postsynaptic neuron. An action potential is generated when the EPSP is large enough to exceed the threshold voltage (–55 mV). Axons a and b are excitatory, and axon c is inhibitory to the postsynaptic neuron.

- When a nerve cell is stimulated, two types of potentials are produced
- 1) When a sub-threshold stimulus is applied to a neuron, it will not produce an action potential but will lead to the development of a localized depolarising potential change that is not conducted and called as **local non-propagating potential.**
- 2) **Propagated potential which is the action potential or nerve impulse**

Conduction velocity of Impulses through Nerve Fibres

- The conduction velocity of an action potential in an axon is proportional to the fibre **diameter in myelinated fibres and with sq. root of fibre diameter in unmyelinated fibres**.
- The diameter ranges from 0.1 mm for the smallest unmyelinated fibres to 20 mm for the largest fibres.
- Hence the conduction velocity in a mixed nerve ranges from 120 m/ sec for the largest myelinated fibres to 0.5m/sec for the smallest unmyelinated fibres.

NERVE FIBRE TYPES

- **Type A and B are myelinated and Type C non-myelinated fibres**

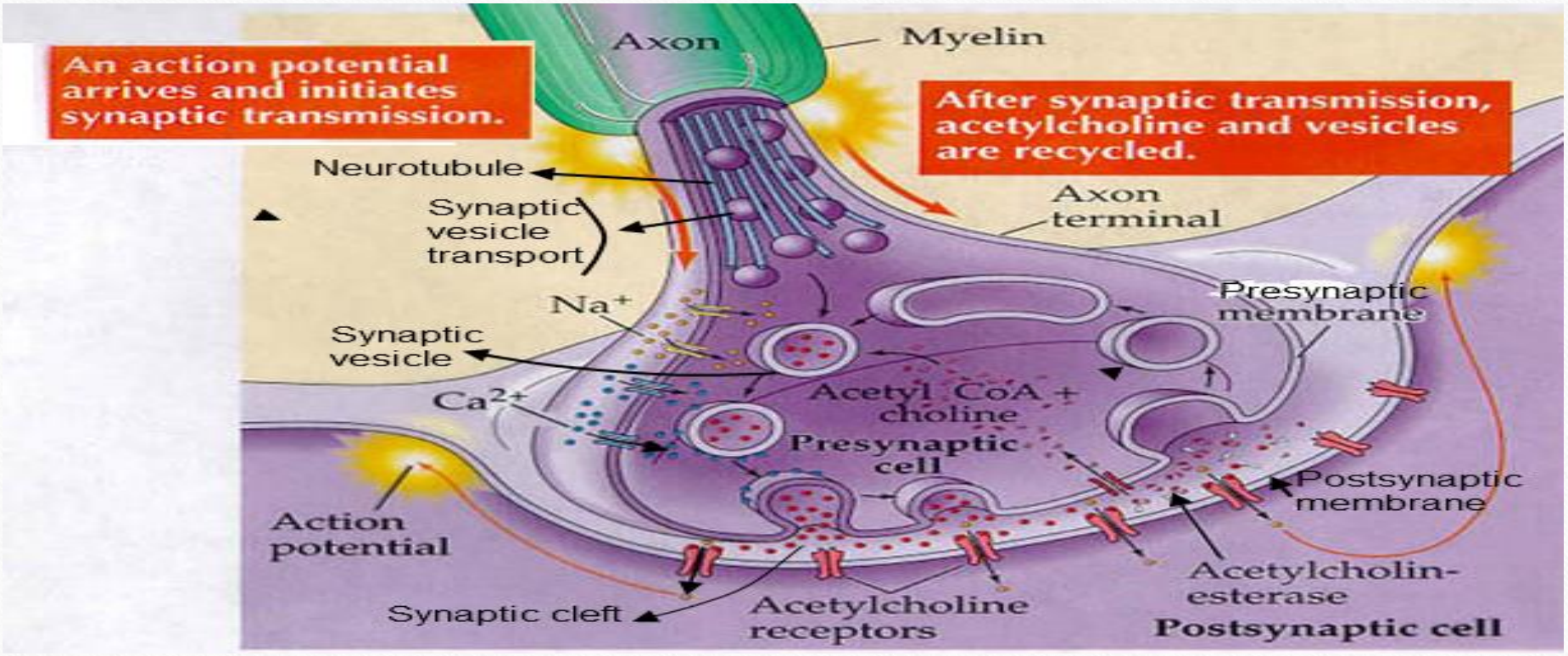
Fibre type	Diameter mm	Conduction velocity m/s
A-a (group I)	12 – 20	70 – 120
A-b (group II)	5 – 12	30 – 70
A-g	3 – 6	15 – 30
A-δ (group III)	2 – 5	12 – 30
B	< 3	3 -15
C (group IV)	0.4 - 1.2	0.5 – 2
Dorsal root fibre	unmyelinated	
C-Sympathetic	0.3 - 1.3	0.7 - 2.3

SYNAPSE

- Synapse is the specialized junctional point between two adjacent neurons through which the impulses from one neuron will be transmitted to the next neuron.
- The transmission of impulses can be effected from dendrite end to the adjacent soma of the same neuron or from axon end of one neuron to the soma of the next neuron.
- When the terminal end of motor neuron forms a junction with the muscle fibres, it is referred as the **neuromuscular junction.**
- ***Types of Synapses*:**
- ***Axosomatic*: Between the axon of one neuron and soma of the next. (spinal cord and autonomic ganglia)**
- ***Axoaxonic*: Between two axons (interneurons of spinal cord).**
- ***Axodendritic*: Between axon of one neuron and the dendrite of other neurons (dorsal horn of the spinal cord).**
- ***Dendrodendritic*: Between the dendrites of different somas (cerebellum).**

STRUCTURE OF SYNAPTIC JUNCTION

- One neuron makes contact with another neuron through the synapse.
- At the synapse, the presynaptic and post synaptic membranes are close to each other and lie parallel to one another, but are separated from each other by a space called as *synaptic cleft*, which has a width of about **20 - 30nm.**
- The presynaptic and postsynaptic membranes are thickened and modified.
- The presynaptic terminal is called as ***presynaptic knob*** **or** ***terminal knob*****, button or** ***end-feet.***
- More number of mitochondria is present in the presynaptic knobs which provide energy for the synthesis of the neurotransmitters.
- The presynaptic knob has numerous storage vesicles called as **synaptic vesicles** for storing the neurotransmitter substances.
- The synaptic knobs are more in number (80-90%) in the dendrites than in the soma (10-20%).


An action potential arrives and initiates synaptic transmission.
Axon
Myelin
After synaptic transmission, acetylcholine and vesicles are recycled.
Neurotubule
Synaptic vesicle transport
Axon terminal
Na+
Presynaptic membrane
Synaptic vesicle
Ca2+
Acetyl CoA + choline
Presynaptic cell
Postsynaptic membrane
Action potential
Acetylcholin-esterase
Synaptic cleft
Acetylcholine receptors
Postsynaptic cell

Difference between NMJ and synapse B/W Neurons

traction of skeletal muscle. The electrochemical events governing the neuromuscular synapse and the synapse between neurons are similar; however, the neuromuscular synapse is somewhat unique in the following respects.

1. One motor neuron innervates a variable number of muscle fibers, forming a motor unit (whereas synapses between neurons are made by numerous other motor neurons, sensory neurons, and interneurons).
2. Action potentials generate only EPPs (whereas synapses between neurons generate both EPSPs and IPSPs).
3. ACh is the only neurotransmitter (whereas synapses between neurons involves many other neurotransmitters, e.g., ACh, glutamate, aspartate, GABA, glycine, 5-HT, substance P).
4. nAChR is the only receptor type (whereas synapses between neurons utilize many other receptors (e.g., muscarinic, NMDA, AMPA).

TYPES OF SYNAPSES

- Based upon the mode of transmission of impulse in the synaptic junction, the synapses are grouped into two types:
- **Chemical synapse**
- **Electrical synapse**

:

General Characteristics of Chemical and Electrical Synapse

	CHEMICAL SYNAPSE	ELECTRICAL SYNAPSE
1	Presynaptic action current has minimal effect (2 to 3 msec) on post synaptic membrane	Presynaptic action current is the immediate agent for synaptic potential. Transmission
2	Post synaptic membrane receptor molecules combine with transmitter leading to ion permeability changes and postsynaptic potential	No such changes
3	Pre (or) postsynaptic membrane may contain hydrolysing enzymes for transmitter inactivation that occur pre or postsynaptically	No such mechanism
4	Trans synaptic conduction is Unidirectional	Commonly bi-directional
5	Trans synaptic action is sensitiveto temperature changes	Relatively insensitive to temperature changes

CHEMICAL SYNAPSE

- When the transmitter-receptor complex opens the cation (mainly Na^+) channels, there will be postsynaptic excitation created by increased permeability to Na^+ ions; this leads to depolarization of the postsynaptic membrane; the potential that is developed is known as **excitatory postsynaptic potential** [***EPSP***]. EPSP brings the postsynaptic membrane potential closer to threshold level for generating action potential

- The opening of the K^+ or anionic channels causes postsynaptic inhibition due to increased Cl^- (or K^+) ion permeability in the postsynaptic membrane leading to hyperpolarization and it results development of **inhibitorypostsynaptic potential *(IPSP)***.

Summation

- Summation of postsynaptic potential occur in two ways
- **Temporal summation** – When the **frequency of presynaptic action potential** is raised, the postsynaptic potential summate to reach threshold level.
- **Spatial summation**– A postsynaptic neuron synapses with **many presynaptic neurons.** When more and more presynpatic neurons are stimulated, the postsynaptic potential reaches threshold for depolarization.

NEUROTRANSMITTERS

- Neurotransmitters are chemicals that are used to relay, amplify and modulate electrical signals between a neuron and another cell.
- The neurotransmitters can be classified into two major groups based on size and action

1) Small molecule - rapidly acting transmitters:

- They are synthesized in the presynaptic terminal and stored in synaptic vesicles, rapidly released during each action potential.
- The synaptic vesicles are recycled over and over again.
- They include the following classes of transmitters

Class I	Acetylcholine	Acetylcholine
Class II	Biogenic amines	Norepinephrine, epinephrine, dopamine, (catecholamines) histamine, serotonin (5 hydroxy tryptamine)
Class III	Amino acids	Glycine, glutamate, aspartate, GABA (Gamma Amino Butyric Acid)
Class IV	Non traditional transmitters	Nitric oxide, ATP, CO

Large molecule long-acting neuropeptide transmitters

- They are slow acting transmitters.
- These peptides are synthesized in the neuronal cell body by ribosomes as inactive precursors which undergo enzymatic cleavage to become pro-transmitter molecule containing the active peptide.
- The proneuropeptide is packaged in Golgi apparatus to form secretory vesicles where the active neuropeptide is produced by enzymatic cleavage.
- The vesicles are actively transported from the cell body through the axon by a slow process called axoplasmic transport (few cm/day), stored in synpatic boutons and released by the process of exocytosis.
- This group includes the following molecules
- **GnRH, TRH, CRH, somatostatin, LH, GH, oxytocin, vasopressin, gastrin, CCK, insulin, glucagon etc.**

Functional Classification:

a)	**Excitatory neurotransmitters:**	**Glutamate, substance P, L-aspartate**
a)	**Inhibitory neurotransmitters:**	**Glycine, GABA, dopamine, serotonin, alanine, morphine, endorphins, enkapalins**
a)	**Both excitatory and inhibitory:**	**Acetylcholine, nor-epinephrine and epinephrine, histamine, prostaglandin (PG)**

Transmitter Action on postsynaptic membrane

- Postsynaptic membrane has specific receptor proteins for binding with the transmitter.
- The action of a transmitter on a postsynaptic membrane depends on the specificity of the membrane receptor-protein activated.
- A postsynaptic neuron usually has more than one type of receptor and more than one type of transmitter can activate the postsynaptic neuron.

Fate of Neurotransmitters

•The duration of activity of the excitatory or the inhibitory transmitters in the synaptic cleft will last for only 1 to 2 milliseconds.

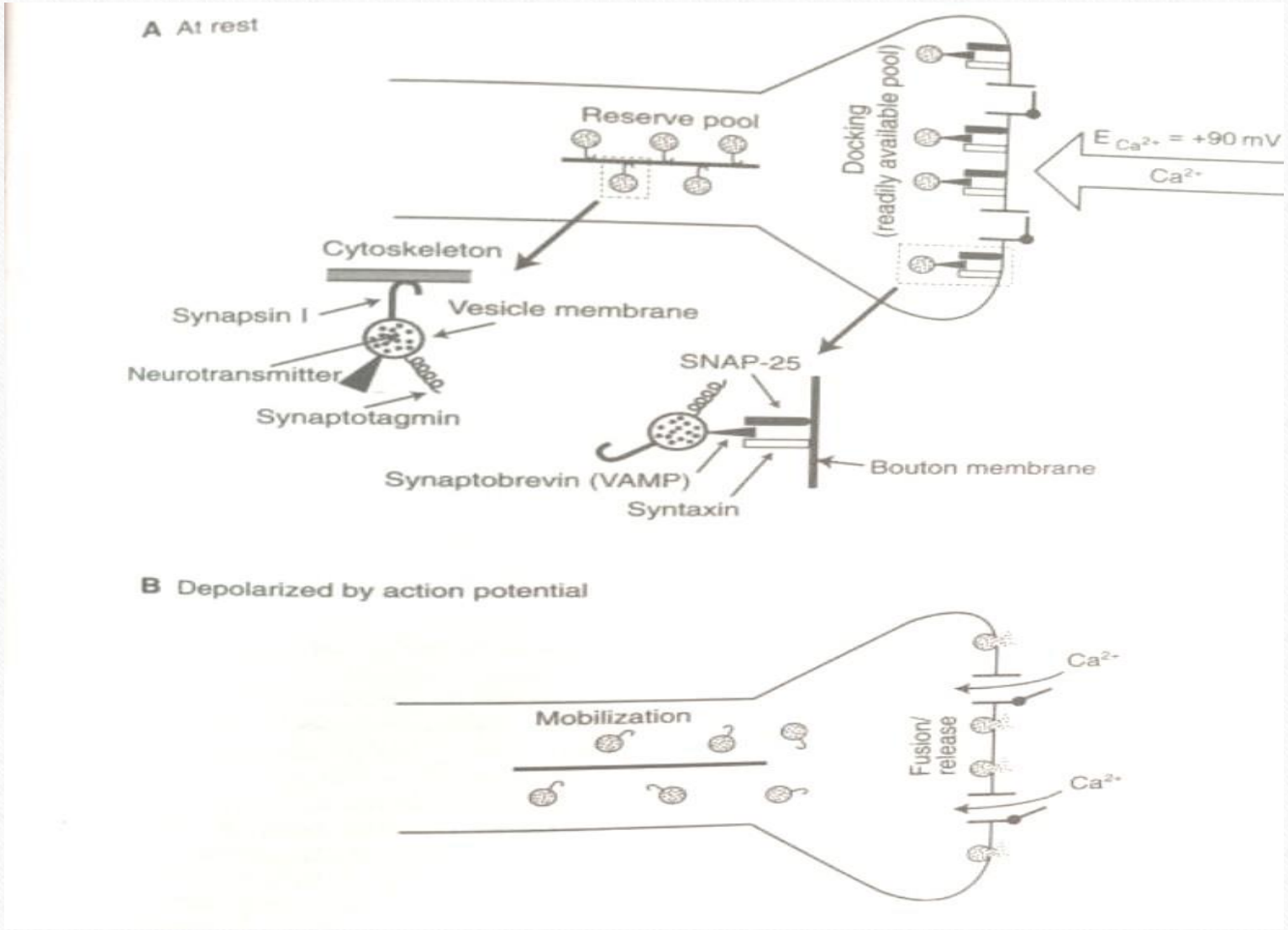
•The following are the reasons for the very short duration of activity of the neurotransmitters on the channel system.

- •Reuptake of the transmitters by the presynaptic knobs
- •Diffusion of the transmitters into surrounding ECF
- •Enzymatic destruction within the cleft

- **Excitatory transmitter:** The transmitter that selectively opens Na^+ channels of the postsynaptic neuron is referred to as **excitatory transmitter**. This channel system form *type-I* of chemical synapse which is common in **axodendritic synapse** (e.g. nicotinic acetylcholine receptors).
- **Inhibitory transmitter:** The transmitter that opens either K^+ or Cl^-channels of the postsynaptic neuron is **inhibitory transmitter** (K^+ moves out of cell or Cl^- enters into the cell) and it inhibits the postsynaptic membrane by causing *hyperpolarization* of the postsynaptic membrane.

Table 43.1. Representative ionic concentrations of mammalian neurons under resting conditions and their approximate equilibrium potentials (E_{ion})

	Ionic concentrations (mM/L)		
	Intracellular	Extracellular	E_{ion} (mV)
Sodium	10	140	+70
Potassium	140	5	−90
Chloride	4	100	−85
Calcium	0.01	10	+90


A At rest
Reserve pool
Docking
(readily available pool)
$E_{Ca^{2+}}$ = +90 mV
Ca^{2+}
Cytoskeleton
Synapsin I
Vesicle membrane
Neurotransmitter
Synaptotagmin
SNAP-25
Synaptobrevin (VAMP)
Syntaxin
Bouton membrane
B Depolarized by action potential
Mobilization
Fusion/
release
Ca^{2+}
Ca^{2+}

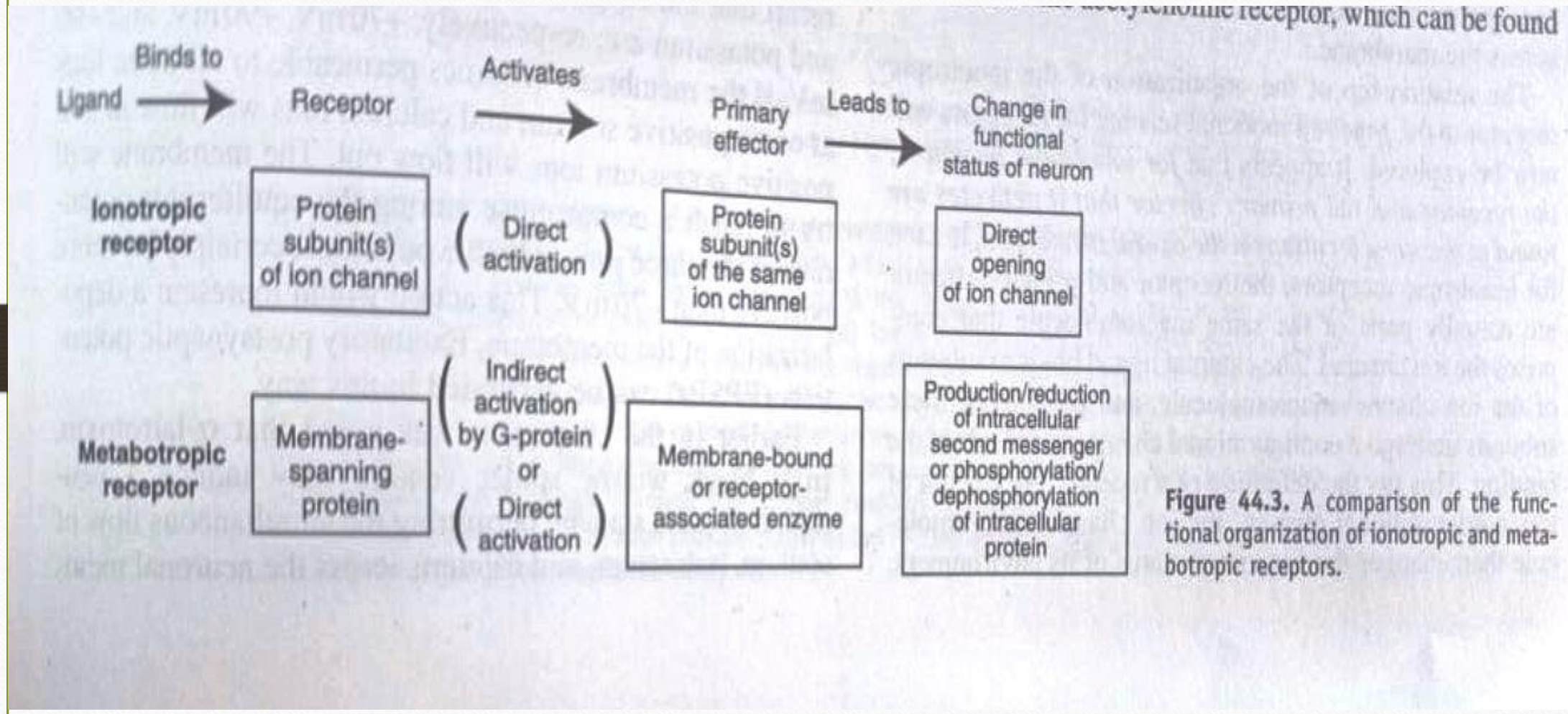


Figure 44.3. A comparison of the functional organization of ionotropic and metabotropic receptors.

Types of membrane receptors

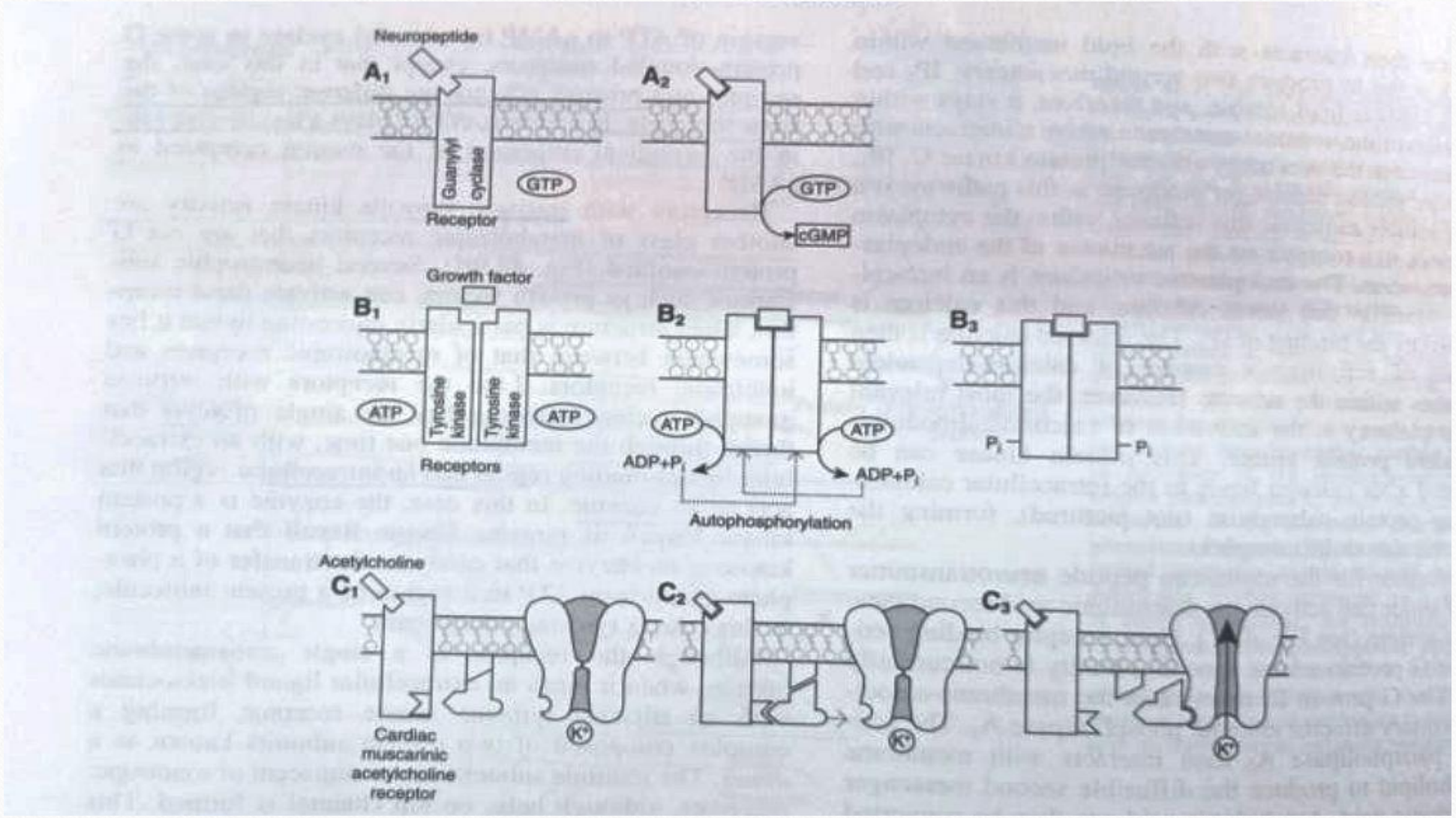
- **Ionotropic receptors**
- **Metabotropic receptors**
- Ionotropic receptors produce direct and rapid changes in ion permeability when the receptor is activated by the transmitter ligand and leads to local changes in membrane potential.
- The metabotropic receptors produce indirect effects which have slower onset but widespread biological action by initiating metabolic changes within the neuron.

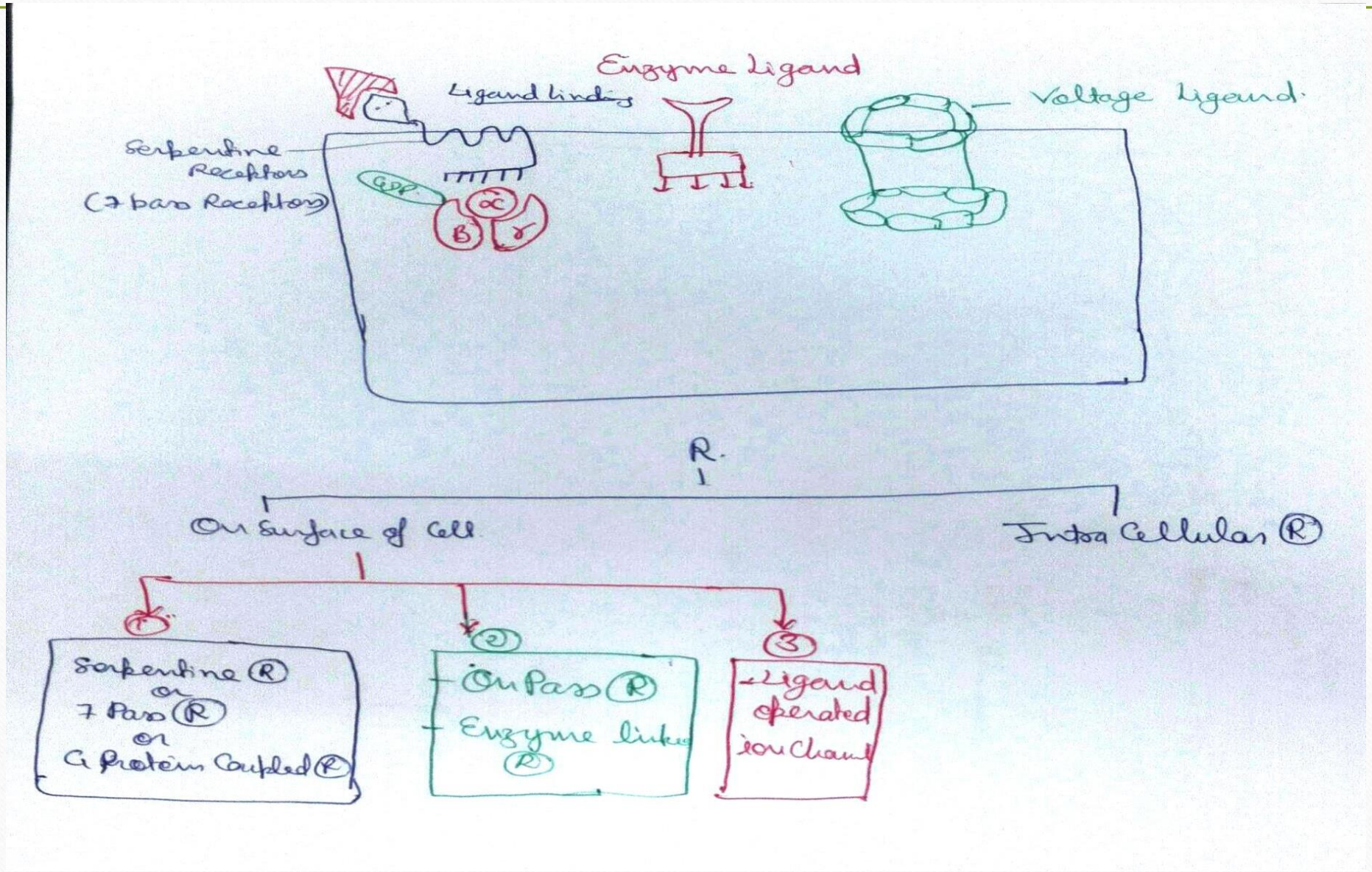
Ionotropic Receptors (Chemically activated ion channels)

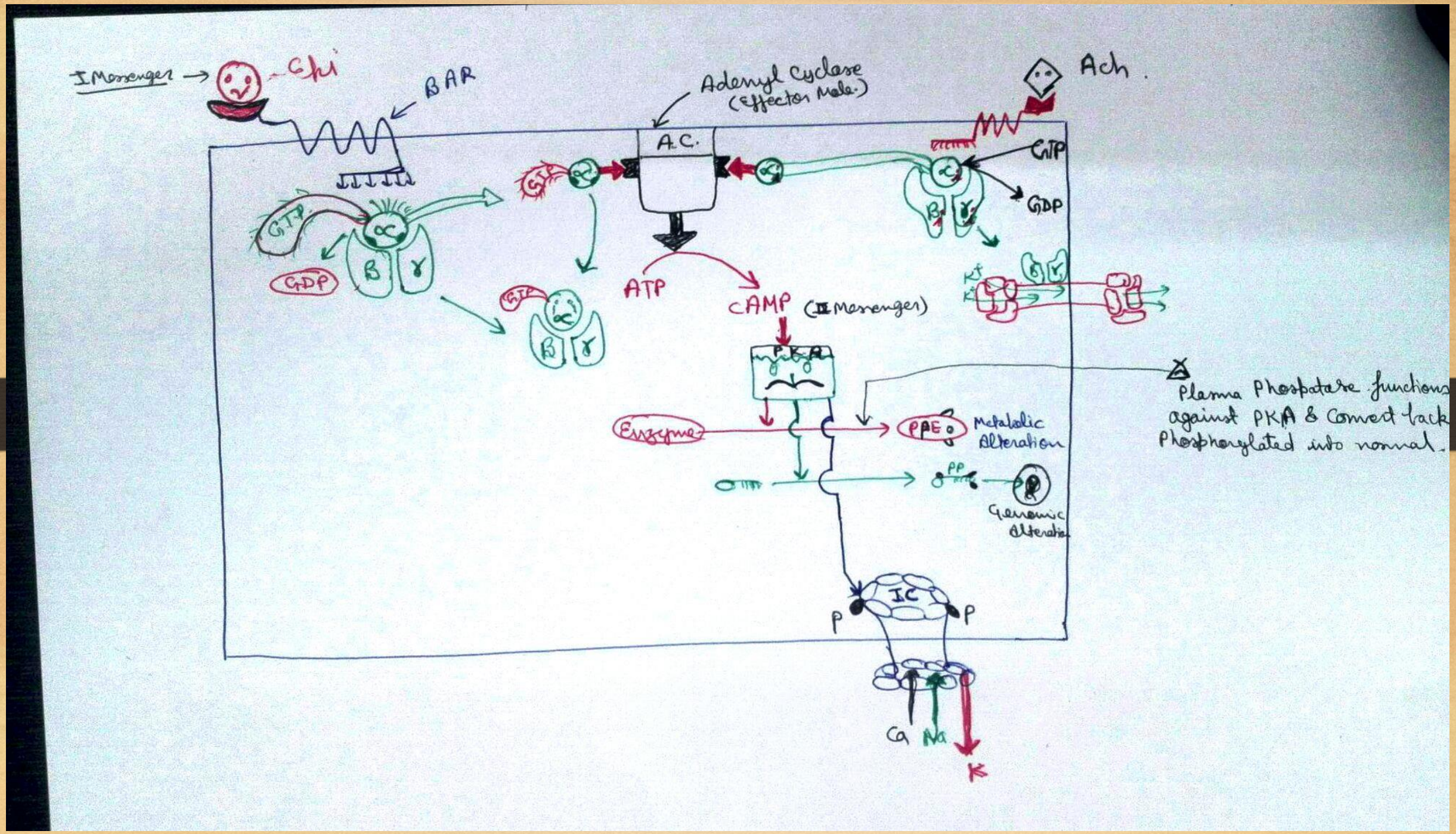
- The ionotropic receptors are ligand-gated ion channels. The opening and closing of these channels is regulated by binding of ligand (chemical) to the receptors. This type of postsynaptic membrane-bound receptor protein has two components –
- **Binding Component** that protrudes from the postsynaptic membrane into the synaptic cleft and readily binds with the released neurotransmitters.
- **Ionophore Component** that protrudes to the interior of the postsynaptic membrane of the neuron.
- There are two types of *ionophores or ion channels*.
  - The ion channels are either cation channels which allow passage of mainly Na^+ and to a lesser extent K^+/Ca^{2+} ions
  - Anionic channels which allows passage of Cl^- ions

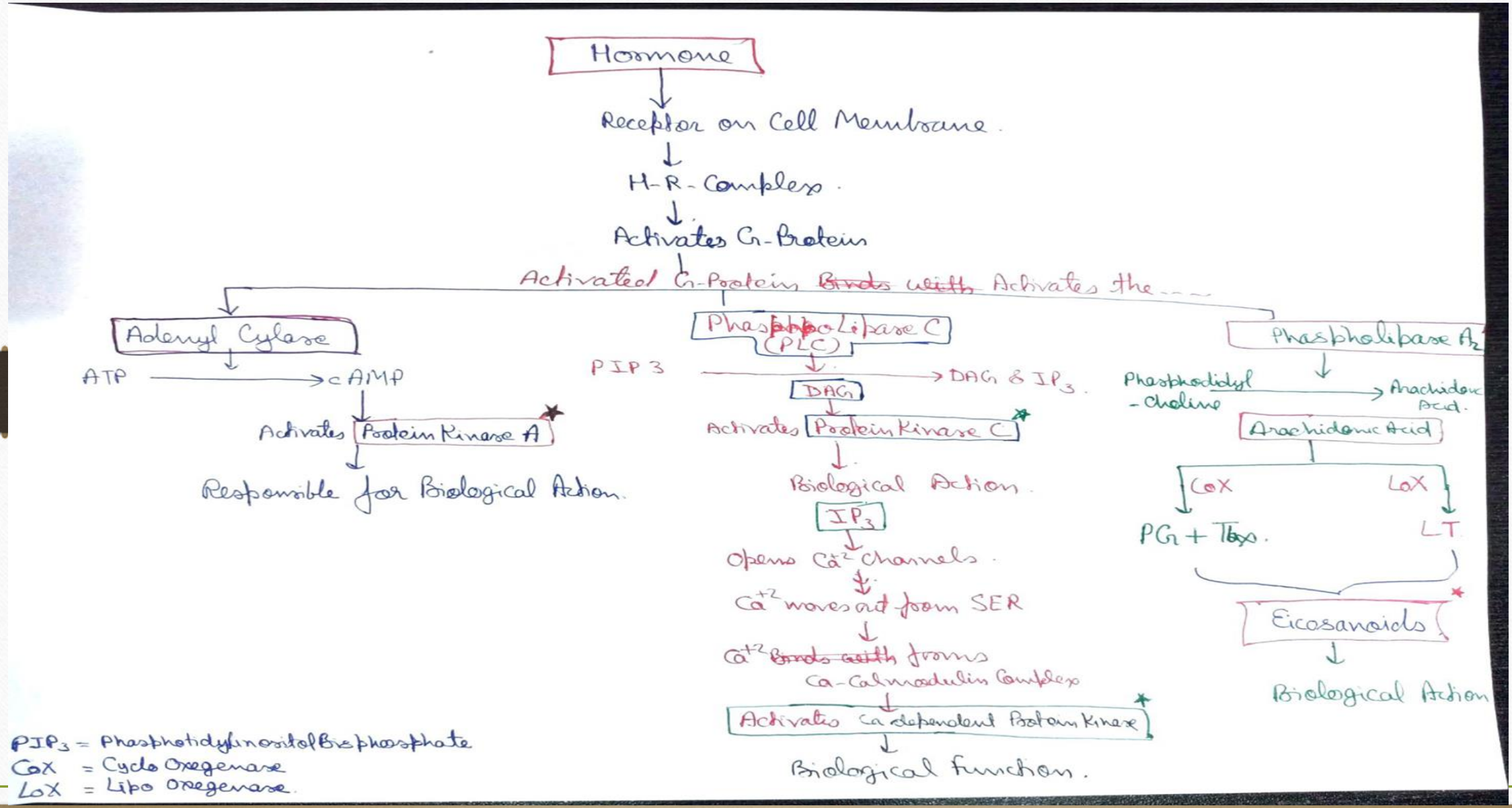
Metabotropic Receptors (Second Messenger Activator)

- When a transmitter binds with metabotropic receptors, the receptors undergo a conformational change which activates an intracellular enzyme that catalyzes metabolic activities of the postsynaptic neuron.
- One type of metabotropic receptors involve a group of proteins called "G" proteins which are attached to the receptor that protrudes into the interior of the postsynaptic cell. On activation of the receptor by the neurotransmitter, a portion of the G protein separates and moves inside the cytoplasm and performs multiple functions as *second messengers*.
- The G proteins cause: (1) activation of cAMP system (2) activate intracellular enzymes (3) activate gene transcription which produces change in postsynaptic cellular function.


Neuropeptide
A1
Guanylyl cyclase
GTP
Receptor
A2
GTP
cGMP
Growth factor
B1
Tyrosine kinase
Tyrosine kinase
ATP
ATP
Receptors
B2
ATP
ATP
ADP+Pi
ADP+Pi
Autophosphorylation
B3
Pi
Pi
Acetylcholine
C1
K+
Cardiac muscarinic acetylcholine receptor
C2
K+
C3
K+


Enzyme Ligand
Ligand binding
Voltage Ligand.
Serpentine Receptors
(7 pass Receptors)
GDP
α
β
γ
R.
On Surface of Cell
Intra Cellular ®
1
2
3
Serpentine ®
or
7 Pass ®
or
G Protein Coupled ®
On Pass ®
Enzyme linke
®
Ligand
Operated
ion Chann


I Messenger
Epi
BAR
Adenyl Cyclase
(Effector Mole.)
A.C.
Ach
GTP
GDP
ATP
cAMP
(II Messenger)
PKA
Enzyme
PPE
Metabolic
Alteration
PP
Genomic
Alteration
IC
P
P
Ca
Na
K
Plasma Phosphatase functions
against PKA & Convert back
Phosphorylated into normal.


Hormone
Receptor on Cell Membrane.
H-R-Complex.
Activates G-Protein
Activated G-Protein ~~Binds with~~ Activates the---
Adenyl Cylase
ATP → cAMP
Activates Protein Kinase A
Responsible for Biological Action.
Phospholipase C (PLC)
PIP 3 → DAG & IP3.
DAG
Activates Protein Kinase C
Biological Action.
IP3
Opens Ca+2 channels.
Ca+2 moves out from SER
Ca+2 ~~Binds with~~ forms
Ca-Calmodulin Complex
Activates Ca dependent Protein Kinase
Biological function.
Phospholipase A2
Phosphatidyl-Choline → Arachidonic Acid.
Arachidonic Acid
COX
LOX
PG + Tbxs.
LT
Eicosanoids
Biological Action
PIP3 = Phosphotidylinositol Bisphosphate
COX = Cyclo Oxegenase
LOX = Lipo Oxegenase.

Clinical implications

•Organophosphorus insecticides have inhibition of acetylcholinesterase activity; Ach level increases following toxicity leading to dysfunction of ANS, skeletal muscles and respiratory failure.

•An abnormal level of monoamines in brain leads to depression – a dietary deficiency of tryptophan decreases brain serotonin level.

•Cocaine and amphetamine block the reuptake of catecholamines back into the terminal.

NEUROMODULATORS

- A **neuromodulator** modulates synaptic transmission - these are the substances released by neurons that modify how other neurons will respond to input.
- The neuromodulator may act presynaptically to change the amount of transmitter released in response to action potential or they may act postsynaptically to modify response to transmitter.
- The neuromodulator can also act as neurotransmitter that is not reabsorbed by the pre-synaptic neuron or broken down into a metabolite.
- Such neuromodulators end up spending a significant amount of time in the CSF and influencing (or modulating) the overall activity level of the brain.
- For this reason, some neurotransmitters are also considered as neuromodulators. Examples of neuromodulators in this category: serotonin and acetylcholine.

Colocalization of neurotransmitter

- Many neurons contain at least two (up to four) neurotransmitters within their synaptic buttons and this is called **colocalization.**
- The large molecule transmitter is colocalized with other members of small or large molecule transmitters and each is stored in separate vesicles.

PERIPHERAL NERVOUS SYSTEM

- **The PNS includes all nervous structures - the peripheral ganglia, spinal nerves, cranial nerves and the autonomic nerves, located out of the brain and the spinal cord.**
- **The PNS functions to provide communication between the sensory receptor organ and the CNS (sensory) and from the CNS and the effector organs (motor).**
- **Peripheral nerves are myelinated.**
- **It is divided into motor (efferent) and sensory (afferent) subsystems.**
- **The motor peripheral nerves that supply to skeletal muscles are referred to as *somatic motor nerves***
- **The motor peripheral nerves that supply the cardiac and smooth muscles and exocrine glands are referred to as *autonomic nerves*.**

•The afferent (sensory) system consists of two divisions: *Somatic* and *visceral.*

•Somatic sensory nerves carry impulses from all sensory systems including mechanoreceptors,chemoreceptors, thermoreceptors, nociceptors,

•photoreceptors (eye), auditory receptors (ear) and stretch receptors (skeletal muscles), whereas the visceral sensory nerves carry visceral sensations from the chest and abdomen.

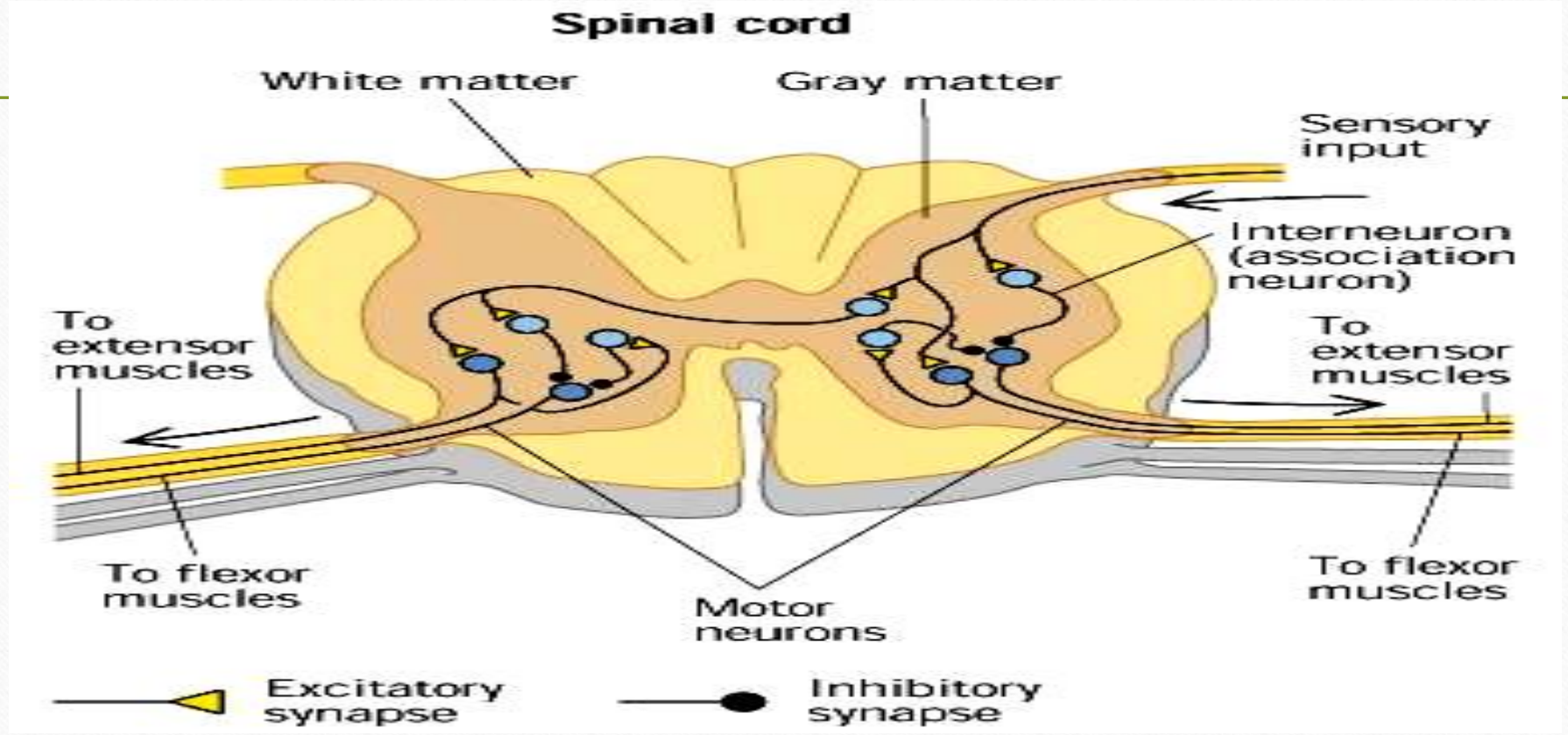
STRUCTURE OF SPINAL CORD:

Spinal cord is a caudal extension of the medulla oblongata present throughout the length of the vertebral canal.

•Each spinal segment provides a pair of spinal nerves that are formed by the fusion of *dorsal root* (sensory) fibres and the *ventral root* (motor) fibres.

•The number of spinal segments (dogs) is: 8 cervical (C1-8), 13 thoracic (T1-13), 7 lumbar (L1-7), 3 sacral (S1-3) and variable number of caudal segments.

•At the centre of the cord, the cellular components form an `H' shaped column known as the *gray matter*. It is surrounded by *white matter* which represents bundles of nerve fibres or *tracts*


Spinal cord
White matter
Gray matter
Sensory input
Interneuron (association neuron)
To extensor muscles
To extensor muscles
To flexor muscles
To flexor muscles
Motor neurons
Excitatory synapse
Inhibitory synapse

•The neurons of the gray matter aggregate together to form *nuclei*.
•The sensory nuclei occupy the dorsal and the lateral columnsof the spinal gray matter
•The motor nuclei are located in the ventral motor columns of the spinal gray matter.
•Sensory signals enter the cord through the dorsal root fibres. After entering the cord, the primary afferent fibre synapses with second order neurons which may be an interneuron, an ascending neuron or a descending neuron.
•The neurotransmitters released at the primary afferent fibre terminals in the spinal cord are glutamate and aspartate (excitatory) or GABA (inhibitory). Substance P is also coreleased with these neurotransmitters to modulate their effect.
•The gray matter of spinal cord has cell bodies (soma), dendrites and axon terminals of the nerves. The axons of the spinal gray matter neurons are mostly nonmyelinated in nature. The axon fibres in the white matter are mostly myelinated fibres

•Receipt of sensory input (dorsal horn)
•Controls the efferent activities of the viscera -autonomic functions; (intermediate zones in the thoracic and lumbar segments).
•Controls the motor neuron activity to skeletal muscle (ventral horn).
•It is concerned with the integration of spinal sensory and motor activities.