NERVOUS SYSTEM PHYSIOLOGY

(a) ***To explain the basic electro-physiology of neural tissue (Eg. resting membrane potential, conduction of nervous impulses, action potentials, excitatory and inhibitory post-synaptic potentials, synaptic function).***

(I) Overview of the nervous system:

Nervous system → coordinates physiological activities of several organs via a network of "neurons"

Consists of two parts:

Central nervous system	Peripheral nervous system

- Includes neurons within the brain and spinal cord	- Includes sensory and motor fibres that enter ("afferent fibres") and leave ("efferent fibres") the CNS or are wholly outside the CNS
	 - Efferent fibres of further divided into:
	     o (i) Autonomic nervous system – "Involuntary" control of visceral function for homeostatic purposes
	     o (ii) Somatic nervous system – "Voluntary" motor function

(II) Excitable Cell:
- A cell that responds to a stimulus by a rapid change in electrical charge of the cell membrane (Eg. nerve cell transmits a signal, muscle cells contracts, gland cell secretes)

(III) Equilibrium (Nernst) potential:
- Defined as the potential difference an ion generates when the membrane is permeable to it, and the net movement of the ion down its "concentration gradient" is equal and opposite to the developed "electrical gradient" across the membrane
- This is determined by the "Nernst equation":

$$V_{ION} = \frac{- RT}{zF} \ln \frac{[ion]_i}{[ion]_o}$$

V_{ION}	= Eqm potential of ion
R	= Universal gas constant
T	= Absolute temperature
z	= Elementary change of ion
F	= Faraday constant
$[ion]_i$	= Intracellular [ion]
$[ion]_o$	= Extracellular [ion]

Or at body temperature:

$$V_{ION} = - 61.5 \log \frac{[ion]_i}{[ion]_o}$$

- Nernst potential of various ions:

Ion	$[ion]_i$	$[ion]_o$	V_{ion}
Na^+	10	145	+ 70 mV
K^+	135	4	- 95 mV
Cl^-	9	125	-80 mV

> Important to note → Membrane potential is EQUAL to the equilibrium potential of an ion IF the membrane is solely permeable to that ion (Ie. K^+ equilibrium potential and RMP)

(IV) Resting Membrane Potential (RMP):

Overview of RMP:
- Defined as the steady state potential difference (measured in mV) that exists across the cell membrane when the cell is in an unexcited state
- RMP of different excitable tissues varies → due to differing ionic permeability of the membrane (Ie. opening states of membrane ion channels) in the respective tissues at rest

Myelinated axon:	-70 mV
Skeletal muscle cell:	- 80 mV
Ventricular myocyte:	- 90 mV
Cardiac pacemaker cell:	- 60 mV

Determinants of RMP: Goldman-Hodgkin-Katz equation
- RMP of a cell can be determined by the (i) concentration gradients and (ii) relative permeability of the various ions (esp Na^+, K^+, Cl^-) across the cell membrane at rest

$$RMP = - 61.5 \, Log_{10} \, \frac{P_K[K^+]_i + P_{Na}[Na^+]_i + P_{Cl}[Cl^-]_o + Etc.}{P_K[K^+]_o + P_{Na}[Na^+]_o + P_{Cl}[Cl^-]_i + Etc.}$$

- It can be seen that the ion(s) that contributes MOST to the MP will have the:
  - ○ (1) Largest membrane permeability
  - ○ (2) Highest [ ] present
  - ○ (3) Largest transmembrane [ ] gradient

Factors that generate RMP:
- (1) K^+ equilibrium potential → MAIN factor
  - ○ K^+ equilibrium potential (-95 mV) is very near RMP of most excitable tissue b/c:
    - ▪ (i) Na^+/K^+ ATPase pumps Na^+ extracellularly and K^+ intracellularly → establishes a large transmembrane [ ] gradient for both K^+ and Na^+
    - ▪ (ii) BUT the cell membrane is very permeable to K^+ cf. Na^+ (by 100x) due to non-gated K^+ channels
    - ▪ (iii) Causes more K^+ to be lost from the cell than Na^+ entering it → produces a net –ve membrane potential 2° to an excess loss of +ve charge

> Note – Although RMP is close to the equilibrium potential of Cl^- (-70 mV), Cl^- is NOT the main determinant of RMP as its concentration gradient is created passively by the electrochemical gradient provided by the Na^+/K^+ ATPase

- (2) Na^+ influx
  - ○ Electrochemical gradient generated by Na^+/K^+ ATPase and impermeability of the cell membrane to Na^+ at rest → produces small intracellular "leak current" of Na^+
  - ○ This causes the RMP to deviate more positively from the equilibrium potential for K^+ → contributes + 8 mV to RMP
- (3) Na^+/K^+ ATPase
  - ○ Primary active transporter is an electrogenic (pumps 3 Na^+ extracellularly; 2 K^+ intracellularly) → contributes – 4 mV to RMP
- (4) Gibbs-Donnan effect
  - ○ Presence of large non-diffusible –ve charge moieties on the inside of cells (Eg. proteins and inorganic phosphates) affects the distribution of permeable ions across the membrane → contributes small amount of RMP

(V) <u>Action Potentials</u>:

"Action Potential" (AP) → large rapid change in membrane potential that occurs in excitable cells

Generation of an AP:

- An AP is triggered when there is a reduction in membrane potential (Ie. becomes more +ve) in a process called "Depolarisation" → this can be induced by exposure to a current
- Initially, this produces electrotonic potentials which are summated to form small changes in membrane potentials that are transmitted locally ("Graded Potentials") → AP is triggered when summation of these potentials reach "Threshold Potential" (~ 55 mV → 10-15 mV above RMP of – 70 mV)

Process of an AP:
- (1) Membrane potential is initially at "resting" state (RMP = -70 mV) → then depolarised to "Threshold potential" (10-15 mv above RMP → ~ -55 mV) where an AP is triggered
- (2) "Rising phase" → membrane potential ↑ rapidly to peak of +35 mV
- (3) "Falling phase" → membrane potential ↓ below RMP to a "+ve phase"
- (4) Membrane potential then rises above RMP temporarily ("Negative after-potential")
- (5) Membrane potential then falls below RMP temporarily ("Positive after-potential") → returns back to RMP
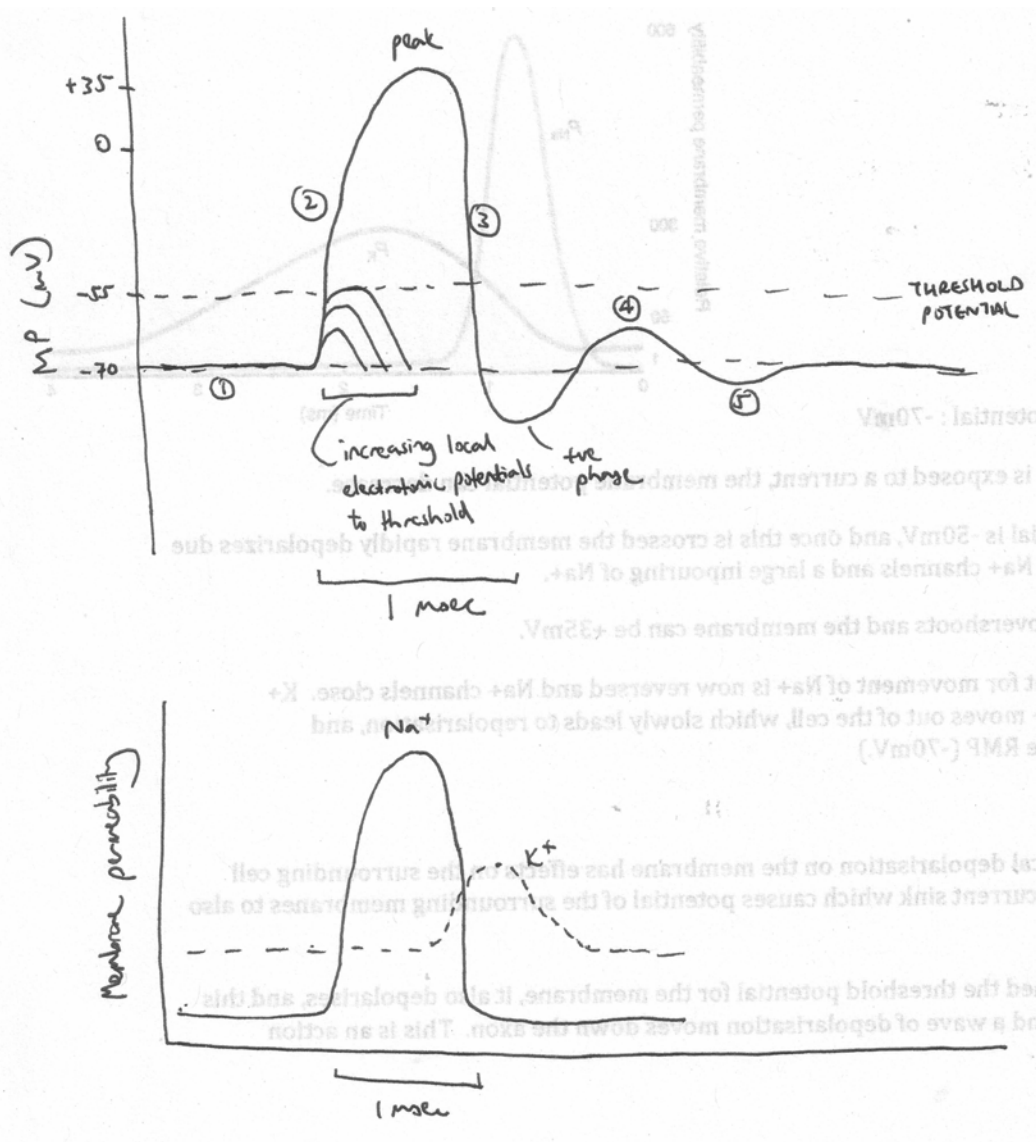
Ionic basis of AP:

Important to note – Changes in MP during an AP occur due to consecutive changes in the membrane's permeability to Na^+ and K^+ (caused by opening of voltage-gated channels) at "Threshold potential" → this is explained by the "Goldman-Hodgkin-Katz" equation – see above)

(1) At "threshold potential":
- (a) Instant opening of "Fast" VG-Na^+ channels:
  - Sudden ↑ in Na^+ membrane permeability → immediate Na^+ influx 2° to its electrochemical gradient across the membrane (–ve charge on inside; $[Na^+]_{OUT} > [Na^+]_{IN}$) → causes MP to move towards "Nernst potential" of Na^+ (PD_{Na} = +50 mV) as per GHK equation → forms "Rising phase" of AP
  - BUT the "Fast" VG-Na^+ channels open very BRIEFLY (~ 1 msec) before closing again → membrane impermeable to Na^+ again → the ↑ in MP falls short of the PD_{Na} → thus, "Peak" of +35 mV is only achieved
- (b) Delayed opening of VG-K^+ channels:
  - Slow ↑ in K^+ membrane permeability → late K^+ efflux due to the electrochemical gradient of K^+ across the membrane (+ve charge on inside; $[K^+]_{OUT} < [K^+]_{IN}$)
  - As the VG-Na^+ channels start to close and VG-K^+ channels becomes fully opened → MP to move towards the "Nernst potential" for K^+ (PD_K = -90mV) as per GHK equation → produces the "Falling phase"
  - Because the VG-K^+ channels are also delayed in closing, the MP falls below RMP (towards PD_K) → results in the "Positive phase"

(2) VG-K^+ channels eventually close and the membrane's permeability to K^+ returns to that of the "Resting" state → MP rises back to RMP

(3) Ion balance across the cell membrane is restored by the Na^+/K^+ ATPase

Characteristics features of AP:
- (1) ALL-OR-NONE phenomenon – Once "Threshold potential" is met, an AP is fired off. If this potential is not reached, there is no AP
- (2) Size of AP is NOT affected by stimulus intensity – Amplitude of APs are all identical!
- (3) Nerve transmission of information is proportional to FREQUENCY of AP (NOT its amplitude!)
- (4) AP is associated with a "Refractory period" where two signals cannot be summated in that period of time

> Important to note → these features are NOT seen with a "Graded potential" (defined as electrotonic potentials summated to form small changes in MPs that are transmitted locally)

Refractory period of AP:
- "Refractory period" → time after an AP where the nerve cell is incapable of generating another AP for a brief period of time
- There are two types:
  - (i) Absolute refractory period – Occurs in first millisecond of a nerve AP when the "Fast" VG-Na^+ channels are still open → during this period, an AP CANNOT occur regardless of the intensity of stimulus applied
  - (ii) Relative refractory period – Occurs within 10-15 ms following the absolute refractory period when the "Fast" VG-Na^+ channels are reset but the neuron is hyperpolarised (Ie. MP is farther from "threshold potential") → thus, AP can be elicited during this period ONLY if the stimulus applied is INTENSE enough
- Role of "refractory periods":
  - (i) Allows unidirectional spread of AP along a nerve
  - (ii) Limits frequency of nerve conduction

(VI) <u>Conduction of nervous impulses</u>:

Process of AP conduction along a nerve:

- (1) Dendrites and soma of the neuron receive neurotransmitter inputs from many pre-synaptic terminals → these inputs generate local electronic currents ("Graded potentials") called "Post-synaptic potentials" (PSPs), which can be either:
    - o (i) Excitatory (EPSP) – Depolarise neuronal membranes by opening Na^+ channels (influx; MAJOR) and K^+ channels (efflux; minor)
    - o (ii) Inhibitory (IPSP) – Hyperpolarise neuronal membranes by opening Cl^- channels (influx) and K^+ channels (efflux)
- (2) AP generation relies on "Summation" of PSPs within the "soma" (cell body) of the nerve → summation can be either:
    - o (1) Spatial – PSPs from multiple synapses are added together at a given moment
    - o (2) Temporal – Consecutive PSPs from a single synapse are added together over a short period of time
- (3) "Axon Hillock" is part of the nerve that has the highest density of VG-Na^+ channels and lowest "Threshold potential" → summated PSPs spread passively here where they will generate an AP and produce nerve conduction when "threshold potential" is reached
- (4) An AP at the "Axon hillock" produces the following events:
    - o When "Threshold potential" is met → large and rapid fluctuations in membrane potential attributed to the consecutive changes in the nerve's membrane permeability to Na^+ and K^+ caused by the opening of voltage-gated channels
    - o Involves (i) early ↑ in Na^+ permeability due to the very brief opening of "Fast" VG Na^+ channels that allow Na^+ influx → causes a rapid ↑ in membrane potential (up to +35 mV), followed by (ii) late ↑ in K^+ permeability due to delayed opening in VG K^+ channels that allow K^+ efflux → causes membrane potential to return back to its "resting" state (-70 to -80 mV)
- (5) Na^+ influx from the AP produces a local electronic current (which is +vely charged) that spreads to adjacent resting membrane (which is –vely charged) → causes them to depolarise to "Threshold potential", thus leading to opening of VG-channels and propagation of an AP → this process repeats itself along the nerve fibre as the AP is propagated
- (6) AP propagation along the axon is UNIDIRECTIONAL as the membrane that was recently depolarised will be in its "Refractory Period" (see above)
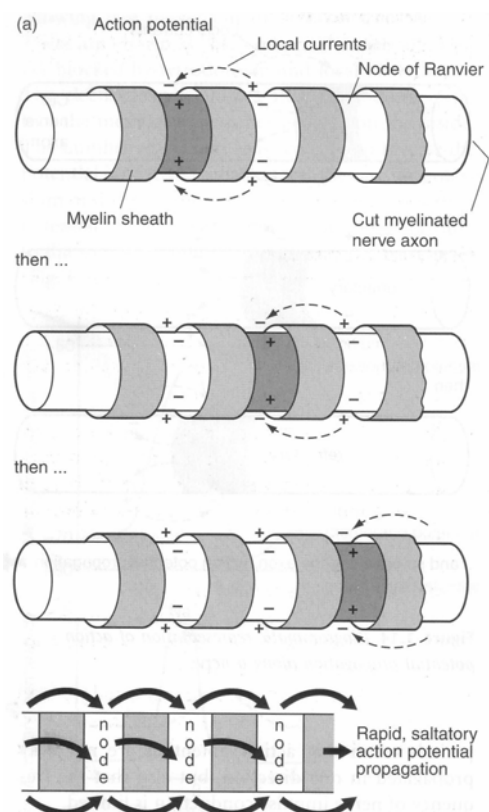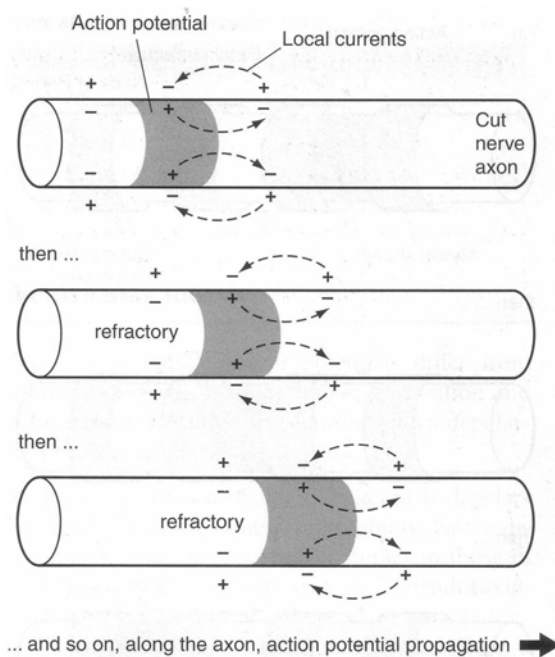
Factors affecting speed of nerve AP propagation:
- (1) Axon diameter:
    o Large cross-sectional area produces low internal axoplasmic resistance to current flow → ↑ speed of nerve AP propagation
- (2) Nerve fibre myelination
    o (i) Unmyelinated fibres – Propagation of AP is a slow and continuous process along the axon from one end to another
    o (ii) Myelinated fibres – Glial cells surrounding the axon (Schwann cells in PNS; Oligodendrocytes in CNS) produce layers of myelin (fatty layer wrapping) at regular intervals along the axon → the spaces between the myelin sheaths are densely populated with VG-Na$^+$ channels ("Nodes of Ranvier") → myelin creates high resistance and low capacitance in the axon's membrane such that local electrotonic current flow through the myelinated parts of the axon unpertubed until its reaches a Node of Ranvier where depolarisation occurs and an AP is generated → causes AP to "jump" from node to node ("Saltatory Conduction") in a unidirectional manner (as the previous node will be in its "refractory period")
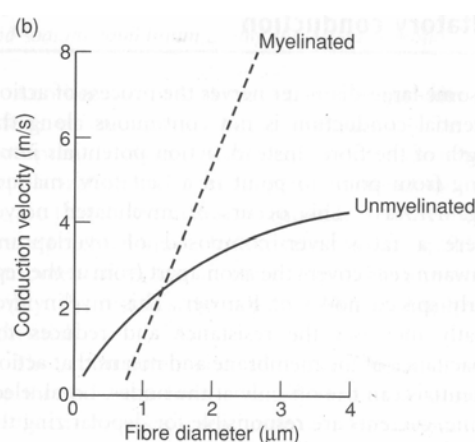

(VII) <u>Overview of neurons and synaptic function</u>:

Overview of a neuron:

"Neuron" is the basic cell unit of the nervous system → highly specialised cell for receiving, processing and transmitting information

Structure:
- (a) Cell body ("soma") – Contains (i) nucleus and (ii) extensive rER system containing basophilic granules ("Nissl substance") that make proteins
- (b) Dendrites – Several branches that leave the cell body to receive information from adjoining neurons → may contain knob-like extensions ("dendritic spines")
- (c) Axon hillock – Part of axon adjacent to soma (where APs are initiated)
- (d) Axon – A single branch leaving the cell body → usually wrapped in myelin with interspersed Node of Ranvier, and contains mitochondria, microtubules, neurofilaments, and SER within it
- (e) Nerve terminal – Contains many small vesicles holding NTs
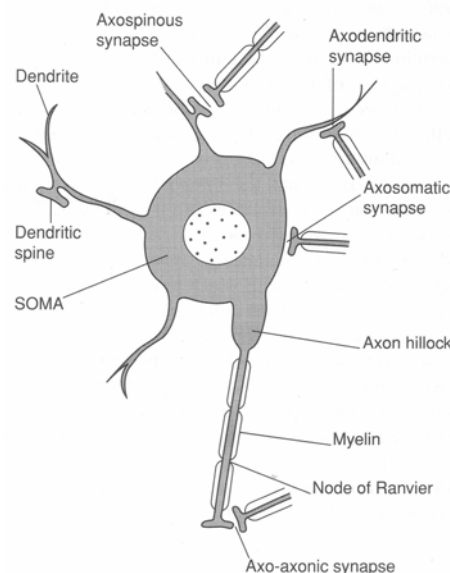
There are two types:
- (i) Projection (Eg. Sensory, Motor) – Large neurons that have long outward projecting axons → generally release excitatory amino acid NTs (Eg. Glu)
- (ii) Interneuron – Small neurons that have short localised axons → generally inhibitory (Eg. GABA)

Overview of synaptic function:

"Synapse" → anatomical site at which chemical or electrical signals are transmitted from one cell to another (Ie. nerve to other nerves, to muscles or to glands) for the purpose of facilitating intercellular communication to generate an effect (Ie. cause muscle contraction, secretion of a hormone, synchronise neuronal activity)

Synaptic transmission can be either:
- (1) Chemical (more common)
  o Has 3 parts – (i) Axon terminal of "Presynaptic cell" (typically of a neuron), (ii) Synaptic cleft (space between cells), and (iii) Membrane of "Postsynaptic cell" (can be another neuron, muscle, or gland)
- (2) Electrical (NOT common)
  o Found in cardiac and smooth muscle (to synchronise contraction), and some nerves (esp at dendro-dendritic sites to synchronise neuronal activity)
  o Formed by "gap junctions" that connect cytoplasm of adjacent cells → facilitates rapid conduction of electrical current between cells

Process of chemical synaptic transmission:
- (1) When a neuron is activated, an AP is generated at the axon hillock and is conducted along the axon
- (2) AP arrives at the nerve terminal and triggers VG-Ca^{2+} channels to open → causes Ca^{2+} influx into the axon terminal and induce vesicle exocytosis → NT is released into the synaptic cleft
- (3) NT then diffuses across the synaptic cleft and binds with receptor on the post-synaptic membrane:
  o These receptors are both – (a) Transmitter specific, and (b) Response specific (either (i) Ionotropic – Opens up ion channels, or (ii) Metabotropic – Signal transduction pathway)
  o NT-receptor binding induces "Post-synaptic potentials", which are a type of "Graded potentials" → either:
    ▪ (a) Excitatory (EPSP) – Depolarise neuronal membranes by opening Na^+ channels (influx; MAJOR) and K^+ channels (efflux; minor)
    ▪ (b) Inhibitory (IPSP) – Hyperpolarise neuronal membranes by opening Cl^- channels (influx) and K^+ channels (efflux)

- (4) Termination of NT activity in the synapse occurs via:
  o (a) Enzymatic destruction of released molecule in synaptic cleft
  o (b) Re-uptake by pre-synaptic cells through specific carrier molecules
  o (c) Receptor/ligand complex internalisation
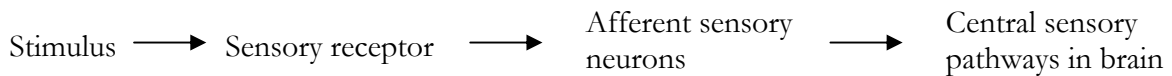
- o (d) Diffusion away from the synaptic cleft

Properties of chemical synaptic transmission:
- (1) Post-synaptic potentials – NT-receptor activity generates "graded potentials":
  - o (a) EPSP ("Excitatory") – Depolarise neuronal membranes by opening Na^+ channels (influx; MAJOR) and K^+ channels (efflux)
  - o (b) IPSP ("Inhibitory") – Hyperpolarise neuronal membranes by opening Cl^- channels (influx)
- (2) A neuron can receive inputs from several other neurons ("convergence") or make synaptic inputs with several other neurons ("divergence")
- (3) "Summation" – Process where synaptic inputs (or PSPs) are added up by the cell body:
  - o (a) Spatial – Summate inputs from multiple synapses at a given moment → if graded potentials of PSP exceed threshold, AP is triggered
  - o (b) Temporal – Summate inputs from a single synapse over time → if graded potentials of PSP exceed threshold, AP is triggered
- (4) Presynaptic inhibition of NT release:
  - o Amount of NT released from axon terminal may be attenuated by presynaptic inhibition by GABA release through axo-axonic synaptic connections with the presynaptic terminal
  - o GABA acts on one of two receptors – Both of which prevent NT release by inhibiting Ca^{2+} influx at the synaptic terminal:
    - ▪ (i) GABA-A receptor – Opens Cl^- channels (influx) → ↓ chance of AP → ↓ Ca^{2+} influx into the nerve terminal and ↓ NT released!
    - ▪ (ii) GABA-B receptor – Acts via G-protein → causes (a) K^+ channel opening (hyperpolarises presynaptic terminal) and (b) Directly prevent Ca^{2+} channel from opening when AP reaches nerve terminal

(b) **To describe the major sensory and motor pathways.**

(I) <u>Sensory pathways</u>:

Structure of sensory pathway:

Stimulus $\longrightarrow$ Sensory receptor $\longrightarrow$ Afferent sensory neurons $\longrightarrow$ Central sensory pathways in brain

(1) Receptors → structures that convert various forms of energy produced by stimuli into nerve impulses

> Types:
> - (i) Superficial somatic receptors (body surface and mucosal membranes) → sense touch, pain, temperature
> - (ii) Deep somatic receptors (muscle, tendons, joints) → sense stretch and movement
> - (iii) Visceral receptors (within walls of blood vessels, gut, bladder, peritoneum) → sense stretch, chemical and pain stimuli

(2) Afferent sensory neurons:
- Enter CNS via (i) spinal cord dorsal roots, (ii) trigeminal nerve and (iii) vagal nerve roots
- Consists of at least 3 neurons – 1° neurons, 2° neurons and 3° neurons → they cross over to the other side of the body and are processed through the Thalamus before arriving at the Somatosensory cortex

> Ascending sensory spinal pathways:
> - (1) Dorsal column
>   - ○ Function – Transmit tactile discrimination, vibration and proprioception
>   - ○ Structure:
>   - ▪ Large myelinated Aβ fibres (1° neuron) has cell body in DRG → axon enters Dorsal column and ascends to the Gracile and Cuneate nuclei to synapse with 2° neurons
>   - ▪ 2° neurons crosses over to opposite site of Medulla to form the Medial lemniscus → terminates at Ventrobasal nucleus of thalamus where they synapse with 3° neurons
>   - ▪ 3° neurons then proceed to the Somatosensory cortex
> - (2) Anterolateral (spinothalamic) tract
>   - ○ Function – Transmit crude touch and pressure (via anterior spinothalamic tract), and temperature and pain (via lateral spinothalamic tract)
>   - ○ Structure:
>   - ▪ Small myelinated Aδ and unmyelinated C fibres (1° neuron) with cell body in DRG → these fibres branch caudally and rostrally in the Dorsolateral tract of Lissauer and then synapse with 2° neurons in Laminae I and V
>   - ▪ 2° neurons decussate to contralateral side of spinal cord → ascend via Anterolateral (spinothalamic) tract to reach Lateral lemniscus → terminate in Posterolateral nucleus of Thalamus where they synapse with 3° neurons
>   - ▪ 3° neurons then proceed to the Somatosensory cortex
>
> > Important to note – Damage to spinal cord on one side produces DISSOCIATED sensory loss:
> > - (i) Loss of dorsal column function on the ipsilateral side
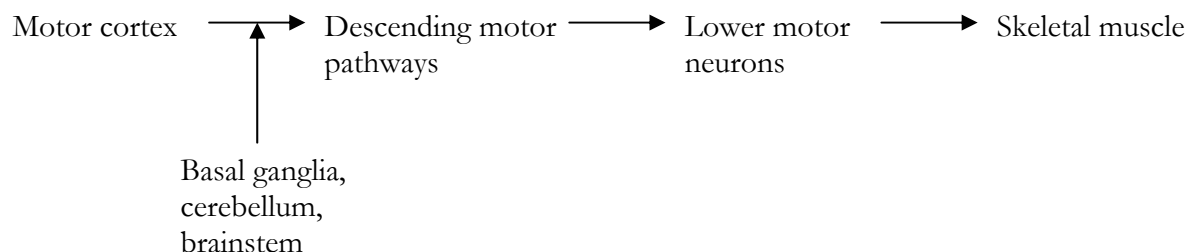> > - (ii) Loss of spinothalamic function on the contralateral side

(3) Central sensory pathways in brain:
- (i) Relay nuclei → role in interaction and modification of sensory input
- (ii) Somatosensory cortex (within parietal lobe)
  - ○ Sensory input from the thalamus is relayed here for final processing/analysis
  - ○ Possesses a "Homonculus" – Somatotopic arrangement whereby each region of the cortex receives input from a specific region of the body (Eg. Foot/leg

represented medially in cortex; face is laterally; arms and trunk located in between) → Nb. certain body areas are disproportionately represented due to variable density of sensory receptors (Eg. lips, fingers)

(II) <u>Motor pathways</u>:

Structure of motor pathway:

Motor cortex → Descending motor pathways → Lower motor neurons → Skeletal muscle

↑

Basal ganglia, cerebellum, brainstem

(1) Motor cortex → generates neural impulses (transmitted via descending motor pathways) for generation of voluntary skeletal muscle activity

(2) Basal ganglia, cerebellum, reticular and vestibular formation in brain stem → modulate neural impulses sent to descending motor pathways (Ie. help maintain postural tone, coordinate limb movement, Etc.)

(3) Descending motor pathways → upper motor neurons of spinal cord

> (a) Pyramidal (Corticospinal) tract:
> - Function – Voluntary control of skeletal muscles → generate precise movements
> - Pathway:
>   o Consists of axons of pyramidal cells in layers III and V from motor cortex → descend through posterior part of the Internal capsule → then through Pons and Medulla
>   o At ventral medulla, axons decussate over to the contralateral side before entering the spinal cord to synapse on a motor neuron cell body in the ventral horn
>
> (b) Extrapyramidal tracts:
> - Function – (i) Maintain postural tone, and (ii) Direct voluntary movements
> - These tracts receive inputs from cerebral cortex, basal ganglia and cerebellum → feed onto interneurons in spinal cord where they exert influence over α- and γ-motorneurons:
>   o (i) Rubrospinal tract → arises from Red nucleus → tract crosses to contralateral side in brainstem then down the spinal cord
>   o (ii) Lateral vestibulospinal tract → arises from Lateral vestibular nucleus → tract does not crossover before going down spinal cord
>   o (iii) Reticulospinal tract → arises from Reticular system in pons/medulla

(4) Lower motor neurons → arise from spinal cord:
- (a) Aα motorneuron – Large cell with large myelinated axons (10-20 um diameter) → innervates extrafusal (contractile) skeletal muscle fibres
- (b) Aγ motorneuron – Small cells with small axons (3-6 um diameter) → innervates intrafusal skeletal muscle fibres

(III) <u>Peripheral nerves</u>:

Overview of peripheral nerves:

- "Peripheral nerves" consist of several myelinated and unmyelinated nerve axons of both sensory and motor fibres held within a connective tissue sheath

> Note – Connective tissue sheath consists of 3 layers → Epineurium, Perineurium, Endoneurium

- These peripheral nerves can be subdivided into fibre types of similar function, diameter and conduction velocity (Erlanger and Gasser classification):

Type	Appearance	Function	Diameter	Conduction velocity (m/s)
A – α	Large peripheral myelinated fibres	Motor	10-20 um	60-120
A – β		Touch, pressure	5-10 um	40-70
A – γ		Proprioception	3-6 um	15-30
A – δ		Pain, temperature, touch	2-5 um	10-30
B	Small myelinated preganglionic ANS fibres in visceral nerves	Preganglionic ANS	1-3 um	3-15
C	Small unmyelinated motor and sensory fibres	Pain/temperature	0.5-1 um	0.5-2

"Compound nerve action potential" of a peripheral nerve:
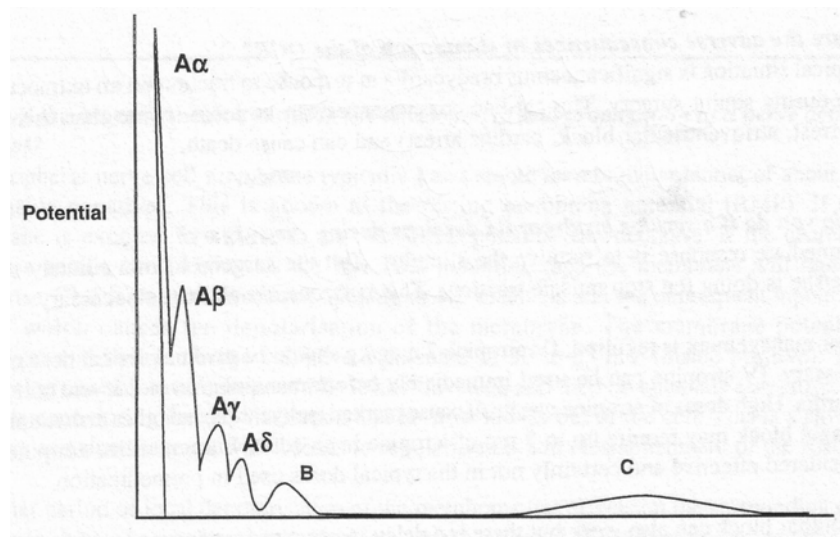
Important features:
- It represents the sum of AP from ALL the axons within the peripheral nerve when a supramaximal stimulus is delivered
- It consists of a series of AP waves of each fibre type within the peripheral nerve → each AP wave represents a group of fibres with similar functions, diameters and conduction velocities (Eg. A fibres, B fibres, C fibres)
- Fibres with highest conduction velocities appear first, while fibres with the slowest conduction velocities appear last
- It is NOT all-or-none phenomenon → each fibre types have a different threshold intensity, hence a supramaximal stimulus is required to stimulate all fibre types within the peripheral nerve
- Of note, NO single nerve contains all fibre types!

(c) ***To describe the physiology of pain with respect to the mediators, pathways and reflexes.***

See "Pain" in pharmacology section of syllabus

(d) ***To describe the physiology of cerebrospinal fluid.***

Overview of cerebrospinal fluid (CSF):
- Clear and colourless fluid contained in ventricles and subarachnoid space → bathes the brain and spinal cord
- Part of body's "transcellular fluid" compartment → specialised component of ECF
- Total CSF volume = 130 mL → 30 mL in ventricles (25 mL in lateral ventricle, 5 mL in $3^{rd}/4^{th}$ ventricles) and 100 mL in subarachnoid space (75 mL in spine and 25 mL in cranium)
- $P_{HYDROSTATIC}$ of CSF = 6.5-20 cmH2O (or 5-15 mmHg) ≈ normal ICP

Functions of CSF:
- (1) Protective role (main function)
    o (a) Water bath effect
        ▪ Brain is fragile as it has little rigidity/mechanical strength → CSF contained within meninges acts as mechanical cushion to prevent brain injury a/w acceleration/deceleration forces 2° to changes in head position and direct head trauma
        ▪ This effect is attributed to the low specific gravity of CSF (1.007) → causes brain to be buoyant → ↓ its effective net weight from 1400 g to 50 g
    o (b) Buffer ↑ ICP by CSF translocation to extracranial subarachnoid space
        ▪ Abrupt ↑ ICP a/w an acute SOL within a rigid and fixed-volume cranium is initially buffered by translocation of CSF within the vault to extracranial compartments
        ▪ When buffer is exhausted (Ie. all CSF translocated) → ICP ↑ very rapidly
- (2) Maintains constant ionic environment conducive to neuronal electrical activity CSF
- (3) Supply role of nutrients (Eg simple sugars, amino acids) and O_2 to brain
- (4) Excretion of toxic substances, metabolic by-products, and CO_2 from brain
- (5) "Lymph-type" function → interstitial proteins in brain ECF return to circulation by CSF absorption across arachnoid villi
- (6) Acid-base regulation → acid-base status of CSF is vital for respiratory control
- (7) Endocrine function → transports hormones to other brain regions

Content of CSF:
- CSF content is IDENTICAL to brain ECF, but differs in several manners from plasma → cf. to plasma, CSF has:
    o (1) ↑ pCO_2 (50 mmHg) → thus producing ↓ pH (7.33)
    o (2) ↓ protein content (0.5% of plasma; 20 mg/dL) → thus CSF has poor acid-base buffering capacity
    o (3) ↓ content of glucose (by 60%) and cholesterol
    o (4) ↑ [Cl] (by 7-14%) and ↑ [Mg^{2+}] (by 40%)
    o (5) ↓ [K^+] (by 40%), ↓ [Ca^{2+}] (by 50%) and ↓ [P_i] (by 20-30%)
    o (6) ↑ creatinine (by 25%) but ↓ urea
- However, they have IDENTICAL osmolality (295), [Na^+] (145), and [HCO_3] (25)

Formation of CSF:

CSF is produced at a rate of 500-600 mL/day → thus, turned over 3-4x each day

CSF is formed at:
- (1) Choroid plexus (> 67%)
    o Plasma in the choroidal capillary is filtered across the fenestrated capillary endothelium via "bulk flow" or "ultrafiltration" (Ie. along $P_{HYDROSTATIC}$ and $P_{ONCOTIC}$ gradients) → BUT the choroidal epithelium is relatively impermeable to this ultrafiltrate due to the presence of apical tight junctions

o Thus, CSF formation across the choroidal epithelium (see diagram below) requires – (i) An actively produced Na^+ gradient (using apical Na^+/K^+ ATPase), (ii) intracellular carbonic anhydrase to facilitate ion flow, (iii) Facilitated transport of solutes (using various apical and basal membrane transporters)
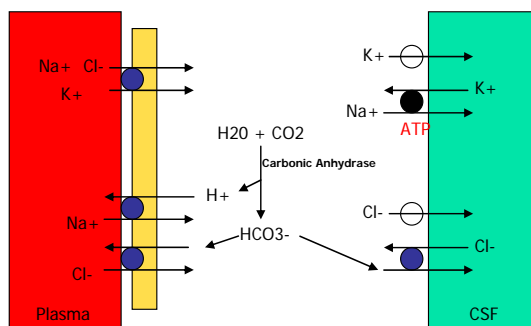
Note:
- (i) Electrolytes – Na^+ enters CSF and K^+ leaves CSF actively against their [ ] gradient; Cl^- and HCO_3^- move passively into CSF down their [ ] gradient
- (ii) H_2O moves from plasma into CSF due to an osmotic gradient
- (iii) Glucose enters the CSF by facilitated transport (Nb. saturated if BGL > 15 mmol/L)
- (iv) Protein enters the CSF via vesicular transport across the cell (but some enters across the tight junction and via extrachoroidal sites)

- (2) Directly from ependymal walls of ventricles (< 33%)

Important to note → "Blood-CSF barrier":
- Physical barrier that prevents freely passage of substances from blood into CSF
- Mechanism – Substances readily pass from blood across the fenestrated choroid plexus capillary endothelium → BUT are prevented from passing into CSF by the apical tight junctions b/t ependymal cells (≈ epithelial cells) of choroid plexus

Nb. It differs form the "Blood-Brain barrier" in that the physical barrier in the BBB that prevents free passage of substances from blood into brain ECF is formed by apical tight junctions b/t capillary endothelial cells (rather than b/t choroid plexus epithelial cells)

Flow of CSF:
- The path of CSF circulation:
  o (i) Once formed within the ventricular system, it circulates within it as follows → flows from lateral ventricles to 3rd ventricle (via interventricular foramen) → then to 4th ventricle (via cerebral aqueduct) → then to subarachnoid space at the Cisterna Magna via the foramens of Magendie (medial) and Luschka (lateral)
  o (ii) It then circulates in the subarachnoid space surrounding the brain and spinal cord
  o (iii) Within the subarachnoid space, CSF is reabsorbed back into the circulation at sites of reabsorption (arachnoid villi and cerebral venules)
- The circulation of CSF occurs by:
  o (i) Ciliary movements of ependymal cells within the ventricular system (MAJOR)
  o (ii) Respiratory oscillations
 o (iii) Arterial pulsations of cerebral arteries

Absorption of CSF:

Excess CSF in the subarachnoid space is absorbed:
- (1) Via arachnoid villi (90%)

- o Arachnoid villi consists of loose arrangements of arachnoid cells with large intercellular spaces → found:
  - ▪ (i) Intracranially (90%) – Within dural walls of sagittal and sigmoid sinuses → drain into Dural venous sinuses
  - ▪ (ii) Extracranially (10%) – Within cranial/spinal nerve root sleeves → drains into lymphatic system
- o CSF flow across them occurs passively via bulk flow down a pressure-gradient (Mean P_{CSF} = 15 cmH$_2$O and dural venous sinus pressure = 9 cmH$_2$O → thus, pressure gradient across villi = 6 cmH$_2$O) → occurs via (i) Pinocytotic transport (1° route), and (ii) Large intercellular openings formed between arachnoid cells
- (2) Directly into cerebral venules (10%)

Balance of CSF formation and absorption:
- Under normal conditions, there is an equilibrium b/t CSF formation and absorption at a certain pressure → this pressure is the "Equilibrium CSF pressure" (or ICP) for that person
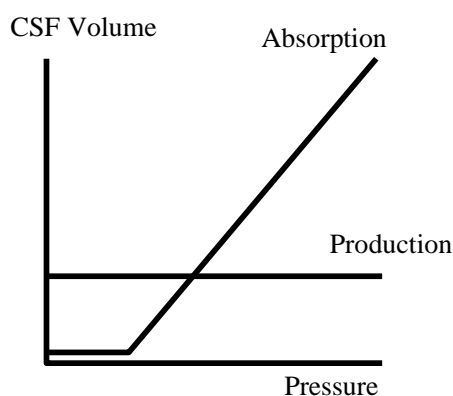
(1) CSF formation:
- CSF is produced at a CONSTANT rate (20 mL/hr) → determined 1°ly by "choroid plexus blood flow" → dependent on factors that determine CBF (esp CPP):
  - o CPP > 70 mmHg → minimal change in CSF production rate
  - o CPP < 70 mmHg → ↓ CSF formation 2° to ↓ CBF
- Note: CSF production rate is NOT affected by Δ in ICP, provided that a ↑ in ICP does not cause CPP to be < 70 mmHg
(2) CSF absorption
- Absorption rate is constant and minimal at low CSF pressures/ICP → BUT ↑ linearly with ↑ CSF pressure/ICP > 6.8 cmH$_2$O (7 mmHg) up to 30 cm H$_2$O (22.5 mmHg)

Aside: Barriers to the Brain

There are two physical barriers that prevent free diffusion of substances between plasma and the extracellular compartment of the brain (Ie. CSF):
- (1) Blood-brain barrier
- (2) Blood-CSF barrier

(I) <u>Blood-Brain Barrier (BBB)</u>:

Location of BBB – Found everywhere in brain, EXCEPT around "circumventricular organs" (see below)

Structure of BBB – BBB is formed 1°ly by endothelial layer of brain capillaries → comprises of a:
- (a) Physical component → capillary endothelial cells (i) possess "tight junctions" (zona occludens) and lack fenestrations b/t adjacent cells (Ie. prevents free passage of substances across barrier) and (ii) have a ↑ mitochondrial content (Ie. substances actively transported across barrier)
- (b) Chemical component → enzymes within capillary endothelial cells (Eg. MAO, DA decarboxylase) degrades toxic substances crossing the barrier

> Important to note – Glial cells (Astrocytes) surrounding the capillaries are NOT part of the BBB, BUT have a role in maintaining it by:
> - (i) Secreting various factors onto the capillary endothelium to support them
> - (ii) Applying foot processes within the perivascular areas around the capillaries → forms intercellular clefts and channels
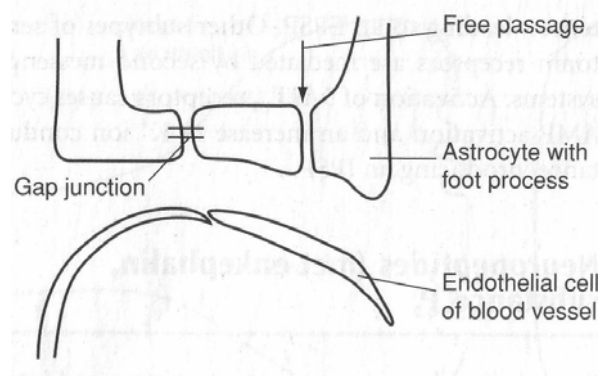
Functions of BBB – Provides a favourable and constant brain ECF content conducive to optimal function of nervous tissue → BBB allows free access to vital metabolic substrates, prevents toxic substances from entering, and helps maintain a constant composition of brain ECF (esp electrolytes)

Permeability of BBB – BBB is a selectively permeable barrier to substances present in plasma:
- BBB is generally permeable to substances that small (MWT < 30 kDa), non-polar and lipophilic → includes respiratory gases (O_2 and CO_2) and H_2O
- BBB is also permeable to other substances by virtue of "active transport" mechanisms (Ie. using specific transporter mechanisms) → includes simple sugars (glucose), amino acids, biogenic amines (5-HT), electrolytes (Ca^{2+}, Mg^{2+}, Cl^-, HCO_3^-, K^+), drugs, Etc.

> Note – BBB is impermeable to polar or lipid-insoluble, charged and large substances

(II) <u>Blood-CSF Barrier (BCB)</u>:

Location of BCB – Found in "circumventricular organs" → small areas of brain surrounding the 3rd and 4th ventricles that lie outside the BBB (choroid plexus, area postrema (CTZ), posterior lobe of pituitary gland, subfornical organs, pineal gland, median eminence of the hypothalamus, organum vasculosm of lamina terminalis)

Structure of BCB – Formed 1°ly by the ependymal epithelial layer → epithelial cells possess "tight junctions" b/t adjacent cells (Ie. prevent free passage of substances across barrier) and are rich in lysosomes (Ie. chemical degradation of substances)

> Important to note – Brain capillaries abutting the ependymal epithelial cell are lined with endothelial cells that are porous with fenestrations (Ie. permit free access of substances) → thus, do NOT form part of BCB)
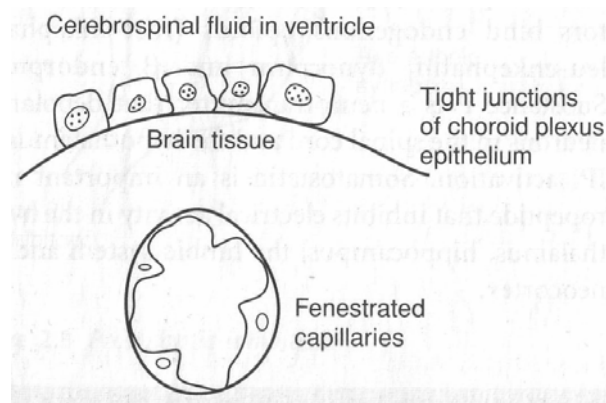
Functions of BCB – BCB's role is to:
- (1) Regulate contents put into newly formed CSF
- (2) Permits release of hormones into CSF (neuroendocrine role)
- (3) Allows sensory analysis of CSF (Eg. CTZ)

(e) **To describe autonomic nervous system and to explain its role in controlling body function.**

See "Pharmacology of the Autonomic Nervous System" in the pharmacology syllabus

(f) **To describe the major neurotransmitters and their physiological role.**

(1) Excitatory amino acids:
- (i) Glutamate → acts via NMDA receptor (fast synaptic transmission via ↑ Ca^{2+} conductance → EPSP) and Kainate receptors (↑ Na^+ and K^+ conductance → EPSP)
- (ii) Aspartate → acts via AMPA receptor (↑ Na^+ and K^+ conductance → EPSP)

(2) Inhibitory amino acids:
- (i) GABA (1°ly in brain) → acts via GABA-A receptor (ligand-gated Cl^- channel → IPSP via ↑ Cl^- conductance) and GABA-B receptor (Gi → IPSP via ↑ K^+ conductance)
- (ii) Glycine (1°ly in spinal cord) → acts via Glycine receptors (ligand-gated Cl^- channel → IPSP via ↑ Cl^- conductance)

(3) Acetylcholine → acts via:
- (a) Nicotinic AChR – Receptor-linked ion channel (pentameric with 2x α and 1x β, γ, δ subunits) → ACh binds EACH α-subunit causing ↑ Na^+ influx and K^+ efflux → depolarises postsynaptic membrane
- (b) Muscarinic AChR – All GPCR (M1 (Gq) → ↓ K^+ conductance and membrane depolarisation); M2 (Gi) → ↑ K^+ conductance and hyperpolarisation); M3 (Gq))

(4) Catecholamines (NAd, Adr, DA) → act via:
- (i) Adrenergic receptors
  - α-receptors – α1 receptors (Gq) and α2 receptors (Gi)
  - β-receptors – β1-β3 (all Gs)
- (ii) Dopaminergic receptors
  - D1 receptors (subtypes D1 and D5) → act via Gs
  - D2 receptors (subtypes D2-D4) → act via Gi or Gq

(5) Indolamines (5-HT) – stored in vesicles of neurons within CNS and PNS → released via exocytosis → acts via:
- 5-HT 3 receptor → produce EPSP due to ↑ Na^+ and K^+ conductance
- Other subtypes of 5-HT receptors are mediated by 2nd messenger (Eg. 5-HT 1A – Gs and AC stimulation, causing IPSP via increased K^+ conductance)

(6) Neuropeptides (Eg. met-enkephalin, substance P, somatostatin)
- (i) Endogenous opioids (Eg. met/leu-enkephalins) → bind opioid receptors
- (ii) Substance P → depolarises neurons in SC and hypothalamus via Gq (DAG/IP3)
- (iii) Somatostatin → IPSP in hypothalamus, hippocampus, limbic system and neocortex

(g) To explain the physiology of the control of intra-cranial and intra-ocular pressure.

(I) <u>Physiology of Intracranial Pressure (ICP)</u>:

Intracranial pressure (ICP) → hydrostatic pressure within the cranial vault → normally 5-15 mmHg

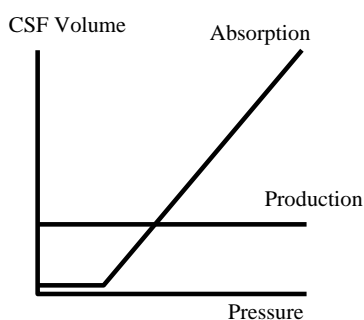> Note – There are rhythmic variations in ICP:
> - A waves (Plateau wave) → due to ↑ ICP (Nb. sneezing, coughing, straining can ↑ ICP to 45 mmHg)
> - B and C waves → due to changes in respiration and arterial pressures

Physiological determinants of ICP:

> "Munro-Kellie Doctrine" → In adults, the rigid and closed cranial vault forms a FIXED brain volume that contains – (1) Brain parenchyma (80%, 1400 g), (2) CSF (10%; 75 mL) and (3) Cerebral blood and vessels (10%; 75 mL) → thus, any change in volume of any one of these components will alter the volume of one or more of the other components of cranial contents

- ICP is determined by the volume of each of these 3 components of cranial content such that a Δ in volume of any one component will affect ICP within this closed system:
   o (1) Volume of brain parenchyma
        ▪ ↑ brain mass with SOL, brain tumour, IC haemorrhage, cerebral oedema
    o (2) CSF volume
        ▪ CSF volume = 150 mL → balanced by rate of production and absorption:
            • (i) CSF production → constant rate of 500-600 mL/day at choroid plexus (67%) and ependymal walls of ventricles (33%) → determined 1°ly by "choroid plexus blood flow" (which depends on factors that determine CBF (esp CPP)):
                o CPP > 70 mmHg → minimal Δ in CSF production rate
                o CPP < 70 mmHg → ↓ CSF formation 2° to ↓ CBF
                o Nb. CSF production rate is NOT affected by Δ in ICP, provided that ↑ ICP does not ↓ CPP < 70 mmHg
            • (ii) CSF absorption → constant and minimal rate at low ICPs at arachnoid villi (90%) and cerebral venules (10%) → BUT ↑ linearly with ↑ ICP > 6.8 cmH$_2$O (7 mmHg) up to 30 cm H$_2$O (22.5 mmHg)
        ▪ CSF acts as a buffer against acute ↑ ICP by translocating to extracranial subarachnoid space
   o (3) Cerebral blood volume → determined by cerebral blood flow (CBF):

$$CBF = \frac{CPP}{CVR} = \frac{MAP - (CVP \text{ or } ICP; \text{ whichever is largest})}{CVR}$$

(CSF Volume / Absorption / Production / Pressure graph)

        ▪ (i) CPP:
            • MAP – Hypotension → ↓ CBF; opposite occurs with hypertension
            • ICP – ↑ ICP 2° to SOL → ↓ CBF
            • CVP – Coughing, straining, vomiting, head-down tilt ↑ CVP → ↓ CBF; opposite occurs with deep inspiration and head-up tilt
        ▪ (ii) CVR:
            • PaCO$_2$ – CBF ↑ 2-4% per mmHg CO$_2$ (b/t 20-80 mmHg) 2° to cerebral vasodilation
            • PaO$_2$ – CBF ↑ only with profound hypoxaemia (< 50 mmHg) 2° to cerebral vasodilation
            • Temperature – Every ↓ 1°C causes ↓ CMRO$_2$ by 8% → ↓ CBF (as cerebral metabolism and CBF are tightly coupled)
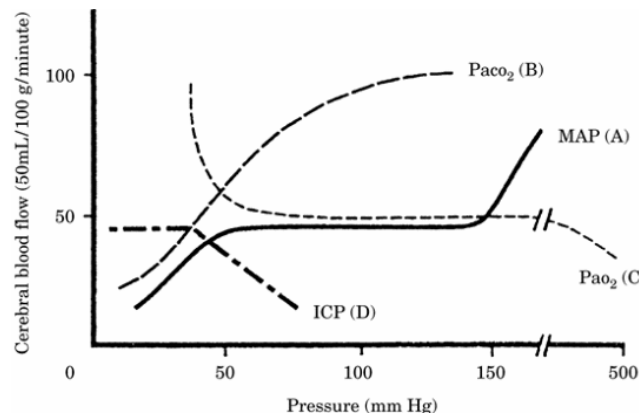
Regulation of ICP:
- "Pressure volume-relationship" can be deduced whereby "Intracranial Elastance" (plots Δ ICP against Δ intracranial volume) is demonstrated, rather than "compliance":

FIGURE 2
VOLUME–PRESSURE CURVE
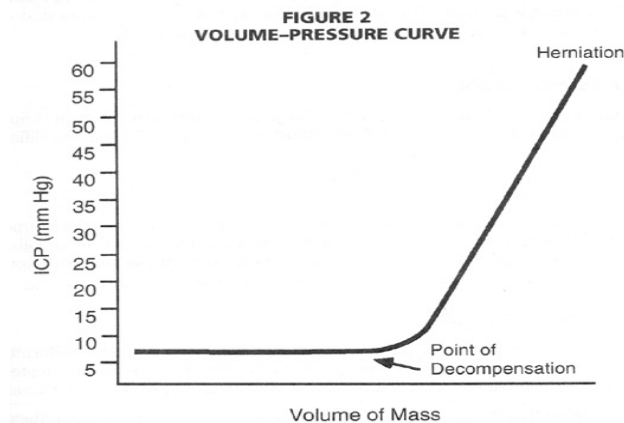
- Within the rigid, closed and fixed volume cranial vault → brain parenchyma and CSF are generally non-compressible, whereas cerebral blood vessels are easily compressed → thus, in the event of ↑ ICP due to alteration in volume of one of the components, there are compensatory mechanisms invoked to minimise it:
  - (i) Initially, there is Δ in CSF distribution and flow → CSF is displaced to spinal subarachnoid space and/or resorption rate ↑'s
  - (ii) Later on → ↓ in cerebral blood volume 2° to ↓ CBF a/w ↑ ICP → leads to cerebral ischaemia
  - (iii) In very late stages → "decompensation point" where all possible structural displacement is exhausted and ↓ in cerebral tissue volume occurs (Ie. brain herniation and death)

(II) <u>Physiology of Intraocular Pressure (IOP)</u>:

Overview of IOP:
- IOP is the fluid pressure within the aqueous humour of the eye → normally 10-20 mmHg, with slight diurnal variation (↑ at night)
- It is kept in this range to maintain eye refractive index (Ie. optimises corneal curvative and spacing of lens/cornea) vital for vision → ↑↑↑ in IOP is a/w ↓ vision 2° to optic nerve damage, corneal opacification, ischaemia of globe structures, glaucoma

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Aside – Aqueous humour:
- Clear and transparent fluid that circulates in the anterior and posterior chambers of the eye → type of ECF (component of transcellular fluid) that is acellular with ↓ [ ] of protein, glucose and urea
- Functions – (i) Provides O_2/nutrients to and removes wastes from avascular lens/cornea, (ii) Produce IOP to maintain the curvature of cornea and spacing of lens/cornea → maintains eye refractive index, and (iii) Remains transparent (does not interfere with light)

Factors determining IOP:

It is important to note that the eye globe is a poorly compliant sphere enclosed within a rigid orbit → thus, small ↑ in volume of globe contents (aqueous humour or blood volume) or external pressures on the globe can lead to significant ↑ in IOP

Physiological determinants of IOP:
- (1) Aqueous humour volume → MAIN determinant

Aqueous humour volume = 0.3 mL → determined by a balance of between:
- (i) Aqueous humour production
  - Aqueous humour is normally formed at a constant rate = 2 uL/min (or 3 mL/day) → turned over 10x each day
  - Two means of formation:
    - (a) Active transport of ions (in a process involving carbonic anhydrase) and subsequent H_2O movement involving epithelial cells of ciliary body in posterior chamber (main process – 66%)
    - (b) Ultrafiltration of plasma from anterior surface of iris (minor process – 33%)
- (ii) Aqueous humour absorption
  - Aqueous humour flows from the posterior chamber around the margin of the iris through the pupil into the anterior chamber → absorbed via two means:
    - (a) Via trabecular meshwork → enters Canal of Schlemm → drains into episcleral venous system (main path – 80%)
    - (b) Via uveoscleral route (minor path – 20%)
  - Absorption occurs via a passive process that is dependent on a $P_{HYDROSTATIC}$ gradient b/t IOP and episcleral venous pressure or scleral interstitial pressure
  - Rate of aqueous humour absorption is variable → main factor that determines aqueous humour volume (and IOP)

- (i) Aqueous humour production:
  - Plasma hypotonicity → ↑ aqueous humour production and volume → ↑ IOP
- (ii) Aqueous humour absorption:
  - Resistance of trabecular meshwork (canal of Schlemm) – Miosis opens up the canal → ↑ absorption → ↓ aqueous humour volume and ↓ IOP; opposite occurs with mydriasis
  - Coughing, straining, vomiting, head-down tilt – impairs venous drainage of episcleral veins → ↓ absorption → ↑ aqueous humour volume and ↑ IOP; opposite occurs with deep inspiration and head-up tilt
- (2) Blood volume within eye globe (esp within choroidal vessels)
  - (i) $PaCO_2$ – Hypercapnoea dilates choroidal arteries → ↑ BV and ↑ IOP; opposite occurs with hypocapnoea
  - (ii) PaO_2 – Profound hypoxaemia dilates choroidal arteries → ↑ BV and ↑ IOP
  - (iii) MAP – Large Δs in arterial BP produce corresponding Δs in IOP
  - (iv) Venous pressure and drainage – Coughing, straining, vomiting, head-down tilt ↑ venous pressure and impair venous drainage → ↑ BV and ↑ IOP; opposite occurs with deep inspiration and head-up tilt
- (3) External eye globe pressures
  - (i) Extraocular muscle tone – ↑ extraocular muscle contraction → ↑ external eye globe pressure and ↑ IOP
  - (ii) Blinking → briefly ↑ external eye globe pressure and IOP by 10-20 mmHg (depending on force)

- o (iii) Sustained external eye globe pressures ↓ globe volume → ↓ IOP when pressure is removed

Pharmacological determinants of IOP:
- (1) Aqueous humour volume:
  - o β-blockers, α-antagonists, CAi (acetazolamide) → ↓ production → ↓ IOP
  - o Cholinergics, PG analogues, mannitol → ↑ drainage → ↓ IOP
  - o Anticholinergics → ↓ drainage → ↑ IOP
- (2) Blood volume within eye globe
  - o Ketamine → ↑ choroidal blood flow → ↑ IOP
- (3) External eye globe pressures
  - o SCh → ↑ extraocular muscle contraction → ↑ IOP

(h) **To describe the integration of central nervous system activity via the cerebellum, hypothalamus, and limbic system.**

(I) Cerebellum:
- It has two key functions:
  - (i) Control of posture, balance, and equilibrium
  - (ii) Coordination of movement

  > Note – It carries out these functions by adjusting the timing, duration and strength of muscle contraction on the ipsilateral side of the body

- Cerebellar cortex has 3 layers:
  - Outer layer: Basket and stellate cells
  - Middle layer: Purkinje cells
  - Inner layer: Granular cells with interneurons ("Golgi cells")
- It possesses three functional lobes:
  - (1) Anterior lobe (part of "paleocerebellum") – Receives input from spinocerebellar tracts → controls muscle tone to maintain posture and equilibrium
  - (2) Posterior lobe (part of "neocerebellum") – Connected to cerebral cortex → controls and coordinates motor function
  - (3) Flocculonodular lobe (part of "archicerebellum") – Connected to vestibular nucleus → controls balance
- The cerebellum receives input from:
  - (1) Cerebral cortex
  - (2) Brainstem (via extrapyramidal tracts and vestibular system)
  - (3) Ascending spinal pathways (via dorsal and ventral spinocerebellar tracts) – Transmit proprioceptive stimuli from muscles, joint, and skin
- It transmits impulses from "cerebellar nuclei" to "brainstem nuclei" then to either:
  - (1) Spinal cord (via descending spinocerebellar tracts)
  - (2) Cerebral cortex (via the thalamus)

(II) Limbic system:
- Formed by parts of both frontal lobes with the following elements:
  - (a) Cingulate gyrus – Arousal reactions and control of movements
  - (b) Hippocampus – Learning, memory and behaviour
  - (c) Amygdaloid body – Fear and rage behaviour
  - (d) Anterior thalamic nucleus
  - (e) Hypothalamus
  - (f) Posterior orbital gyrus – Invokes ANS reactions (esp CVS, respiratory and GI systems)
  - (g) Periamygdaloid and prepyriform cortical areas – Connected to olfactory organs (olfactory sensations)

(III) Hypothalamus:
- An important neuro-endocrine regulation centre of internal organs of the body → it controls (i) autonomic functions, and (ii) hormonal output from the pituitary gland
- It is divided into four functional regions:

Region	Anatomy	Functions
Anterior hypothalamus	Contains Supraoptic and Paraventricular nuclei → give rise to Hypothalamo-hypophyseal tract to the posterior lobe of Pituitary	(1) Controls the PNS (MAJOR) (2) ADH release → SON has osmoreceptors that release ADH in response to ↑ plasma osmolality

		(3) Oxytocin release from PVN (4) Heat-loss mechanisms (5) Induction of sleep
Medial hypothalamus	Contains Ventromedial and Dorsomedial nuclei	(1) Controls energy balance (2) Controls sexual behaviour (3) Inhibition of appetite
Lateral hypothalamus	Contains Tuberal nuclei and Medial forebrain bundle → carries efferent pathways from hypothalamus to the brainstem	(1) Emotional reactions (2) Defence reactions
Posterior hypothalamus		(1) SNS outflow (MAJOR) (2) Vasomotor centre of brain (3) Controls alert/wake state (stimulated by "ascending reticular system")

Note – Limbic system (via anterior cingulate, posterior orbital gyrus, hippocampus and amygdaloid nucleus) has overall control of the hypothalamus → alters CVS, respiratory and GIT activity

(i) **To describe the physiology of sleep.**

(I) <u>Consciousness</u>:

Definition → state of being aware of one's surroundings, own thoughts and emotions

> Note: EEG of conscious state → irregular, high-frequency, low voltage and asynchronous waves

Mechanism:
- Consciousness is brought about by intact cerebral hemispheres interacting with the "ascending reticular activating system" (consists of brainstem, midbrain, hypothalamus and thalamus) → level of activity of this interaction determines the level of consciousness
- Process:
  - (i) "Reticular formation" within pons and medulla contains two nuclei – (a) Locus coerulus (NAd neurons) and (b) Raphe nuclei (5-HT neurons)
  - (ii) These nuclei influence the activity of "Thalamic pacemakers" (Intralaminar and Anterior thalamic nuclei)
  - (iii) These pacemakers alter cortical neuronal activity to cause consciousness by:
    - (i) Exciting cerebral cortex directly → directly cause consciousness
    - (ii) Excite inhibitory interneurons linked to thalamic nuclei a/w drowsiness → indirectly cause consciousness by attenuating drowsiness

> Note – Loss of consciousness suggests either:
> - (i) Lesions diffusely affecting cerebral hemispheres
> - (ii) Lesions directly affecting the reticular activating system

(II) <u>Sleep</u>:

Definition → a physiologically necessary state associated with the reversible loss of reactivity to surroundings and diminished reflexes and awareness, from which the individual may be aroused

There are two types of sleep phases:

	Paradoxical (Random eye movement or REM) sleep	Slow wave (Non-REM) sleep

CNS	- EEG → resembles an alert adult – Rapid, low-voltage, and irregular (desynchronised) activity
	- Active dreaming
	- Rapid eye movements
	- ↑ threshold for arousal
	- $CMRO_2 \approx$ awake state
		- EEG → 4 stages that gradually generate more synchronised, lower frequency, and high amplitude waveform:
		  ○ Stage 1 (person goes to sleep) – α wave replaced by low-amplitude and low-frequency θ wave (4-6 Hz)
		  ○ Stage 2 – Bursts of high-frequency α-like waves called "Sleep spindles"
		  ○ Stage 3 – High amplitude but lower frequency δ waves (1-2 Hz) with bursts of rapid waves (K complexes) superimposed
		  ○ Stage 4 – δ waves become higher amplitude, lower frequency, and synchronised
		- ↓ $CMRO_2$

CVS	- HR irregular and variable - BP varies	- ↓ HR (by 10-30%) - ↓ BP (due to venous pooling 2° to loss of muscle pump)
Respiratory	- ↓ MV and ↓ TV (more cf.	- Progressive ↓ MV 2° to ↓ RR and TV

	non-REM sleep) - RR is irregular and variable - Hypoxic and hypercapnoeic ventilatory drive blunted - ↑ AWR 2° to ↓ muscle tone → OSA	- ↓ FRC 2° to ↓ muscle tone - Hypoxic and hypercapnoeic ventilatory drive blunted (but less cf. REM sleep) - ↑ AWR 2° to ↓ muscle tone → OSA (but less cf. REM sleep)
Muscle	Marked ↓↓↓ skeletal muscle tone (due to ↑ activity of reticular inhibitory area of medulla), with occasional muscle twitches	↓ skeletal muscle tone
Metabolic	- ↑ production of GCs - ↓ metabolic rate - ↓ body temperature	- ↓ metabolic rate - ↓ body temperature
Generation of sleep pattern	"REM sleep centre" is situated in "Pontine reticular formation": - Large phasic "Ponto-geniculo-occipital" (PGO) spike waves produced by the pons generates cholinergic outflow → this antagonises NAd and 5-HT nuclei (locus coeruleus and raphe nuclei) in the Pontine reticular formation that are responsible for consciousness → this outflow then passes rapidly to Geniculate body → then to Occipital cortex	Three zones (cortical and subcortical) responsible for non-REM sleep: - (1) Diencephalic sleep zone (Posterior hypothalamus, and intralaminar/anterior thalamic nuclei) – Low frequency stimuli produces sleep (cf. high frequency stimuli produce consciousness) - (2) Medullary synchronising zone (Medullary reticular formation) – Low frequency stimuli produces sleep (cf. high frequency stimuli produce consciousness) - (3) Forebrain sleep zone (Preoptic area) – Stimuli of any frequency produces sleep

Cycling of sleep phases:
- When a person goes to sleep, they enter non-REM sleep initially and progress from stage 1 to 4 in sequential order → then REM sleep → then back into non-REM sleep in reverse sequential order
- This non-REM to REM cycle repeats itself at intervals of 90 minutes → REM sleep duration is variable (5-30 mins), with non-REM sleep duration taking up the remaining time during 90 mins interval
- During sleep, there are ~ 4-6 REM periods per night (especially towards the early morning) and the frequency of stage 3 and 4 diminishes towards the early morning (Ie. more stage 1 and 2)

(j) **To outline the basis of the electroencephalogram.**

Electroencephalogram (EEG) → recording of spontaneous electrical activity of the brain

Basis of EEG:
- EEG measures the spontaneous electrical activity of the brain generated by a superficial layer of pyramidal cells within the cerebral cortex → measures changes in postsynaptic potentials (EPSPs and IPSPs) in dendrites of pyramidal cells oriented perpendicular to cortical surface generated in response to rhythmic discharges from thalamic nuclei
- These tiny electrical potentials are modified by bone and soft tissue of the head (Ie. produce small but definable differences in potentials) before they are recorded by scalp electrodes → then processed by low and high frequency filters (to remove artefact, such as muscle activity) → then amplified and displayed on either 8 or 16 channels
- EEG is then analysed for – (i) Frequency and amplitude of electrical activity, and (ii) Recognition of wave patterns

Types of EEG waves:
- There are 3 basic types of activity:
  o (i) Continuous and rhythmical
  o (ii) Transient
  o (iii) Background activity
- EEG is usually symmetrical in both hemispheres and represents a combination of different waveforms that differ by their frequencies:
  o (1) Delta wave (< 4 Hz) – Often seen in non-REM sleep
  o (2) Theta wave (4-8 Hz) – Often seen in non-REM sleep
  o (3) Alpha wave (8-13 Hz; peak 10 Hz)
     ▪ Dominant in awake adult at rest with eyes closed and mind wandering, but disrupted with activity, mental stimulation, or opening eyes
     ▪ Most prominent present in the parieto-occiptal area → induced by Thalamic nuclei (pacemaker) activity that vary their firing rates in response to brainstem activity
  o (4) Beta wave (> 13-30 Hz):
     ▪ Seen during conscious effort → unaffected by eye closure
     ▪ Most prominent in frontal area → originates from precentral gyrus and posterior cortex
  o (5) Gamma oscillations (30-80 Hz)
     ▪ Seen when aroused and focused attention on something
- In general, there are two main patterns seen:
  o (i) Awake/alert and REM sleep state – Irregular (asynchronous) low voltage (30-80 uV) waves of high frequency
  o (ii) Deep sleep state (non-REM) – Regular (synchronised) high-voltage waves of a low-frequency

Clinical use of EEG:
- EEGs can only detect damage to the cerebral cortex since electrical potentials measured originate from cerebral cortical tissue (Ie. subcortical tissue damage produces minimal changes in EEG only)
- There are 3 types of EEG abnormalities:
  o (i) Generalised excess of slow wave activity (Eg. infective or metabolic encephalopathy)
  o (ii) Focal excess of slow wave activity (Eg. focal abnormality)
  o (iii) Abnormal electrical discharge of high voltage (Eg. epileptiform disturbance)

> Note: Cerebral ischaemia and EEG – Causes loss of high frequency (Alpha and Beta) waves, and an appearance of large voltage, slow waves (Delta) → prolonged ischaemia will produce low-voltage slow waves, followed by an isoelectric wave