Ho Medical
ANAESTHESIA

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Neurophysiology

1991 Write short notes on the axonal membrane

1. Basic neuron structure:

    a. Axon: a fibre like structure that leaves the cell body and contains mitochondria, microtubules, neurofilaments and smooth endoplasmic reticulum. It starts at the axon hillock and ends at a terminal which contains vesicles of neurotransmitters. It is important for the initiation and propagation of action potentials to cell synapses.

2. Membrane structure:

    a. Cell membrane: phospholipid bilayer which separates the inside of the cell (cytoplasm) from the extracellular environment. It consists of 2 layers of phospholipids with polar heads on the outside and lipophilic tails on the inside. They hold the membrane proteins.
    b. Ion channels: 3 types
        i. Open channels: ion always in the open state, responsible for the fluxes of ions when the neuron is in the resting state. There are more K channels, and hence the membrane shows selective permeability towards K (100x Na).
        ii. Voltage-gated channels: selective channels which are sensitive to the voltage difference across the membrane. They are closed at RMP, and open when threshold potential is reached during DP. They are the main channel found in the axon.
        iii. Ligand-gated channels: either direct ligand gated ion channels, or G-protein coupled channels. Found predominantly in dendritic spines, dendrites and cell bodies.
    c. Nodes of Ranvier: some neurons are myelinated, whereby specialised cells (Schwann cells – PNS, oligodendrocytes – CNS) wrap myelin (protein-lipid complex) around the axon. Nodes of Ranvier are gaps in the myelin sheath which occur periodically along the axon, which contain ↑ concentration of voltage-gated ion channels (2000-12000). Myelin acts as an insulator to action potential conduction, and aids in ↑ speed of conduction (salutatory conduction) and ↓ ion fluxes required for AP propagation.

3. Electrical properties:

    a. As the membrane allows the flow of ions between the ICF and ECF, it acts like an electrical circuit.
    b. Properties:
        i. Conductance – ease with which ions flow across the membrane
        ii. Resistance – inverse of conductance. ECF has a low longitudinal resistance, the axoplasm has a high longitudinal resistance.
        iii. Capacitance – ability of membrane to store electrical charge.

4. Synapse:
    a. Axo-axonal
    b. Axodendritic
    c. Axosomatic
    d. Axospinous

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Physiol-09A12/02A5/96A4 Outline the factors contributing to the generation and maintenance of the resting membrane potential.

1. Resting membrane potential is the voltage difference across a cell membrane at which the electrical and chemical gradients are balanced.

2. Generation of RMP:
    a. Selective permeability of ions:
        i. Open non-gated channels: selective ion channels which are always in the open state and allow passage of ions down their concentration gradient. There are 100x K ion channels compared to Na channels, hence the membrane is more permeable to K.
        ii. Nerst-Potentials: is the voltage difference across the cell membrane for an ion if it were completely permeable. The Nerst potentials for K and Cl are close to RMP, indicating that membrane permeability to great (compared to Na).
        It can be calculated from the Nerst equation:

$$\mathbf{E} = \frac{\mathbf{RT}}{\mathbf{zF}}\ \mathbf{Ln}\ \frac{[\mathbf{ion}]_\mathbf{o}}{[\mathbf{ion}]_\mathbf{i}}$$

        iii. Goldman-field equation: modification of Nerst equation which allows calculation of the RMP based on the relative permeability of the ions.

$$\mathbf{RMP} = \mathbf{58log_{10}}\ \mathbf{P_k}\frac{\mathbf{K_o}}{\mathbf{K_i}} + \mathbf{P_{Na}}\frac{\mathbf{Na_o}}{\mathbf{Na_i}} + \mathbf{P_{Cl}}\frac{\mathbf{Cl_i}}{\mathbf{Cl_o}}$$

        Where P is the relative conductance as a fraction of total membrane conductance, and 58 = RT/F.
    b. Ionic concentrations on the inside and outside of the cell.

Ion	**K**	**Na**	**Cl**
C_{IN} (mmol/L)	150	15	10
C_{OUT} (mmol/L)	5	145	125
Nerst potential (mV)	-90	60	-70

    c. Na-K ATPase pump
        i. Electrogenic membrane-spanning pump which uses ATP as energy to pump $3Na^+$ out and $2Na^+$ in, thus contributing to a negative charge inside the cell.
        ii. Maintains and contributes – 4mV to overall RMP.
        iii. 2 units:
            1. α - larger, ATPase activity (intracellular side), digoxin binding site (extracellular)
            2. β – smaller
    d. Intracellular protein anions (Donnan effect): proteins and organic phosphates have a negative charge, exist in higher concentrations intracellularly and are non-diffusible. This causes a small electric gradient which causes redistribution of diffusible ions across the membrane.
3. RMPs of different cells:

Cell	**RMP (mV)**
Axon	-70
Skeletal muscle	- 90
Cardiac myocytes	-80
Cardiac pacemaker	Prepotential -60
Smooth muscle	Unstable RMP -20 to -60

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1994 Draw a graph of a nerve action potential and outline its physiological basis

1. The peripheral nerve action potential:
    a. Parameters –
        i. RMP = -70mV
        ii. Threshold = -55mV
        iii. Peak = 20-30mV
        iv. Duration = 1-2ms

2. Physiological basis:
    a. Resting membrane potential maintained by–
        i. Maintained by:
            1. Different perm abilities of the cell membrane to sodium and potassium. The membrane is 100x more permeable to K, so ↑ K out of cell and ↓ Na into cell → negative membrane potential.
            2. Differing concentrations of Na and K
            3. Na/K pump setting up gradient across membrane
            4. Intracellular proteins exerting Donnan effect

    b. Ionic fluxes:

Phase	**Description**	**Potential**	**Ion flux (voltage gated channels)**
1	Latent period – resting membrane potential	-70mV	Na/K ATPase pump and leaky channels to Na and K (predominantly) causing RMP
2	Depolarisation – stimulus increases MP to threshold causing positive feedback DP to + 30mV	-55mV threshold to +30mV	Opening of Fast Na channels – rapid influx (positive feedback)
3	Repolarisation to RMP	+30mV to -70mV	Rapid closure of fast Na channels, reversal of Na flow. Opening of K channels – slower efflux (negative feedback)
4	After-hyperpolarisation beyond RMP	<-70mV	Ongoing K efflux due to slow closure of K channels.
5	Return to RMP	-70mv	K channels close Additionally, Ca affects threshold levels for AP. ↓ Ca → ↓threshold → ↑ excitability

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Physiol-97A5 What is saltatory conduction and what are the advantages of this type of conduction?

1. Saltatory conduction describes the propagation of an action potential in a myelinated neuron whereby the AP jumps from node to node.

2. Anatomical description:

    a. Axons in the CNS/PNS are coated with myelin – a lipoprotein complex:
        i. CNS – oligodendrocytes
        ii. PNS – Schwann cells
    b. Myelin sheath wraps nerve several hundred times around, and is interrupted at regular intervals (every 1-3mm) by gaps (1-2µm) called Nodes of Ranvier, which contain dense populations of ion channels (fast Na channels).

3. Physiological description –
    a. AP propagation
        i. RMP -70mV
        ii. Current raises MP to -55mV (threshold) → opening of fast Na-channels → depolarisation to +35mV
        iii. Repolarisation by closure of Na channels, and opening of K channels (K efflux).
    b. Non-myelinated: Local membrane depolarisation acts as a current sink → triggers adjacent threshold potential → depolarisation wave
    c. Myelinated: myelin is a lipoprotein which has insulating properties (↑ resistance, ↓ conductance). Thus it does not participate in depolarisation → ↑ distance of current sink to the next node Ranvier → nodal depolarisation in a jumping manner.

4. Advantage:
    a. ↑ velocity of conduction x 5-50 → ↓ diameter of nerve required for fast velocity
    b. Conservation of ion fluxes (100x less ions required) for AP propagation → conserve energy of ATP pumps to re-establish RMP gradient

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Physiol-96B1 Explain briefly the physiological mechanisms whereby an action potential arriving at a synapse might not be conducted.
1990 Write short notes on synaptic transmission

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1. The synapse is the anatomical site where nerve cells communicate with other nerve cells, muscles and glands. In humans, almost all cells communicate via chemical synapses. It consists of a:
    a. Presynaptic terminal: containing vesicles of neurotransmitters, released by exocytosis. Exocytosis triggered by Ca^{2+} influx through voltage gated ion channels in response to AP from the axon.
    b. Synaptic cleft: space where NTs diffuse and bind to receptors on post-synaptic membrane,
    c. Post-synaptic membrane: binding of the NT to membrane receptors leads to a change in channel permeability (ligand-gated ion channels).
    d. The above processes allow a presynaptic AP to be converted into a chemical signal, which can initiate a new AP in the post-synaptic cell. This takes 0.5ms. Failure of conduction can occur at any of the above anatomical structures.

2. Presynaptic Terminal:
    a. Direct: ionic conductance causing membrane hyperpolarisation → failure to propagate AP (can't reach threshold) → failure of Ca release
        i. ↑Cl conductance → $GABA_A$
        ii. ↑ K conductance → $GABA_B$
    b. Indirect:
        i. Depletion of NT stores in vesicle due to repeated stimulation

3. Synapse: failure of neurotransmitter to cross the synapse
    a. ↑ breakdown (AChE breaks down ACh)
    b. Diffusion NT away from synapse
    c. ↑re-uptake (5HT, NA reuptake)

4. Post-synaptic inhibition:
    a. EPSPs:
        i. Absolute RF: Na channel in the open, inactive state → unable to be activated by any electrical stimulus (1ms, length of AP)
        ii. Relative RF: Na channel in the closed inactive state → can only be activated by a supra-maximal stimulus (10-15ms)
        iii. Failure to reach threshold: summation of pre-synaptic stimuli does not reach threshold for DP. This can be due to inadequate receptor occupancy, or cancelation by IPSP.
    b. IPSPs: binding of NT to receptor causes post-synaptic hyperpolarisation and failure of conduction.
        i. Ligand-gated channels: $GABA_A$ → ↑Cl conductance
        ii. GPCR: M_2 receptor, $GABA_B$ → ↑ K conductance

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Physiol-03B15/98A8 Briefly describe the NMDA (N-methyl d-aspartate) receptor and its physiological role in the central nervous system.

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1. N-methyl-D-aspartate receptor is an important ligand-gated voltage dependent ion channel, which is important in the CNS for glutamate-mediated CNS excitation. It is associated with a family of glutamate receptors which includes – AMPA, kainite, and neurokinin receptors.

2. Anatomy:
    a. Structure – transmembrane 5 subunit receptor with a central cation ionophore
    b. Location: abundant throughout brain and SC on post-synaptic membranes → dorsal horn, hippocampus, cortex.
    c. Activation:
        i. Contains a central Mg^{2+} plug which blocks the channel at rest
        ii. Glycine binding and voltage stimulus (via activation of adjacent AMPA and neurokinin receptors) are required to remove the Mg plug before glutamate binding can open the channel (priming).
        iii. Opening of channel → cations (Ca / Na in, K out) enter /leave the cell → EPSP

3. Physiological role: NMDA receptors are important in transmission and modulation of chronic pain at and above the level of the SC. They are not thought to play any role in normal pain.
    - Ongoing stimulation of slow pain (C) fibres in the SC (lamina II, dorsal horn) → ongoing release of glutamate → displacement of Mg and NMDA receptor activation

    a. Long-term modulation: ongoing stimulation of NMDA receptors produces intracellular changes:
        i. Early gene induction → C-Fos
        ii. NO production → induction and maintenance of chronic pain → positive feedback
        iii. 2^{nd} messenger system activation → ↑ activation of excitatory nociceptive pathways → PKC → ↑ NMDA activity (positive feedback)
    b. Wind-up: repeated stimulus causes ↑ response from dorsal horn neurons mediated by release of excitatory neurotransmitters → dorsal horn neurons are more sensitive to other input → hyperalgesia and allodynia.
        i. ↑ field size
        ii. ↑ magnitude, duration of response to nociceptive stimuli
        iii. ↓ threshold of response to normal stimuli
    c. Long term potentiation: NMDA activation → expression of C-fos → long-lasting neuronal behaviour accounting for neuronal plasticity and memory in the hippocampus and cortex. This is thought to account for long term changes in the body's response to nociceptive input.
    d. Cell death: NMDA activation → ↑ Ca^{2+} influx → cell death via apoptosis. This is seen post-CVA.

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Physiol-08A13/94/91 Describe the production of cerebrospinal fluid, its role and its fate.

1. Cerebrospinal fluid bathes the brain and spinal cord, and is part of the body's transcellular fluid compartment.

2. Function:
    a. Mechanical protection: CSF is a fluid cushion than protects the brain from mechanical injury due to acceleration/deceleration forces. It s low specific gravity (1.007) provides buoyancy which ↓ effective brain weight 1400 → 50g.
    b. Buffering ICP: as the brain, CSF and blood are located in a fixed cranial volume, ↑ volume of any component (SOL) will ↑ ICP (Munro-Kellie doctrine). The CSF can be translocated from vault → SC which buffers any rise in ICP (normal 5-15mmHg).
    c. Protein return to circulation: since there are no lymphatics in the brain, interstitial protein is reabsorbed into the circulation through the arachnoid villi via the CSF.
    d. Ionic environment: BBB contains active pumps to tightly regulate ionic environment for optimal brain activity → Ca, K, Mg, HCO_3^-
    e. Acid base: changes in CSH pH in response to pCO_2 are important in the control of respiration. This is aided by its low protein content → low buffering capacity → ↑sensitivity of pH to pCO_2.
    f. Metabolic:
        i. Nutritional: sugars, amino acids, CO_2, O_2 transported
        ii. Removal of toxins and waste from brain

3. Production:
    a. Volume: 150mL
    b. Formation: 500-600mL/day (3-4x turnover)
    c. Location: 70% choroid plexus, 30% ependymal cells lateral ventricles → foramen Munro → 3rd ventricle → aqueduct of Sylvius → 4th ventricle → foramina of Luscke and Magendie → cistern magna → subarachnoid space of brain and SC.
    d. Process:
        i. Filtration of capillary blood into choroid plexus stroma → protein rich ultrafiltrate.
        ii. Passive diffusion: O_2, CO_2, water, HCO_3 (formed by carbonic anhydrase in ependymal cells), Cl^-,
        iii. Facilitated diffusion: glucose,
        iv. Active transport: Na
    e. Factors:
        i. Not dependent on ICP
        ii. Constant rate, except CPP < 70mmHg → ↓ perfusion choroid plexus → linear ↓ production CSF

4. Absorption:
    a. Location: 90% subarachnoid villi (dural walls of sagittal, sigmoid sinus and dural sinusoids of dorsal nerve roots), 10% cerebral venules
    b. Process: villi function as one-way valves allowing CSF flow down pressure gradient (CSF pressure 11mmHg > venous pressure 7mmHg). Transport across endothelium of villi occurs via pinocytosis.
    c. Factors: rate of absorption constant at lower pressures, but increases linearly as CSF pressure > 5mmHg, ICP > 7mmHg.

5. Composition:

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Substance	**CSF**	**Plasma**
Na	140	140
K	2.9	4.0
Cl	124	110
Ca	1.15	1.65
Mg	1.12	0.8
Glucose	3.7	5
Protein	0.18	80
pH	7.32	7.4
pCO_2	50	40
Chol	↓↓	↑↑

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Physiol-10B14/09A9/04A15/97B3/96/95B6 Discuss the physiological factors that determine intracranial pressure (ICP), and describe how changes in posture affect ICP.

1. Intracranial pressure is the pressure inside the cranium
    a. Normal value 5-15mmHg, < 10mmHg children, and < 5mmHg infants.
    b. Clinical importance: sustained ICP > 25-30mmHg → ↓CPP → CBF → ischaemia, swelling, herniation, death.
    c. ICP not static

2. Munro-Kellie Doctrine – states that the cranial vault is a rigid container with a fixed total volume consisting of:
    a. Brain 85%
    b. CSF 10%
    c. Blood 5%

    As such, any rise in volume of one of these compartments will result in a sharp ↑ ICP unless there is a compensatory decrease in another component. The relationship between pressure change/volume change is given by the Elastance.

3. Factors affecting ICP:
    a. Brain volume:
        i. ↑ Mass (tumour, SOL, generalised swelling) → ↑ volume → ↑ICP

    b. CSF volume:
        i. Normally 150mLs (75mLs brain, 75mLs SC)
        ii. Production: determining factor is CBF to choroid plexus
            1. 500mLs produced per day
            2. Autoregulation can occur when ↑ ICP → ↓ CPP < 70mmHg → ↓ production
        iii. Reabsorption:
            1. Positive relationship with ICP between ICP 7-22.5mmHg due to one-way valve absorption in villi, maintaining ICP-CVP gradient 1.5mmHg.
            2. ↑CVP (venous outflow obstruction) → inhibits reabsorption of CSF → ↑ICP
        iv. Obstruction drainage (hydrocephalus) → ↑ CSF volume → ↑ ICP

    c. Blood volume: directly related to CBF

$$\mathbf{CBF} = \frac{\mathbf{MAP} - \mathbf{ICP}}{\mathbf{CVR}}$$

    There is a positive relationship between CBF, CBV and ICP.
        i. Cerebral PP factors:
            1. ↑MAP → ↑CBF → ↑ICP → ↑MAP (vasomotor system reflex) → viscous cycle
            2. Cardiac cycle: MAP rises during systole, falls diastole → ICP does same (transmitted pressure wave)
            3. Intrathoracic pressure – ICP falls with inspiration, rises with expiration. Expiration/Valsalva/cough → ↑ ITP → ↓VR → transmitted venous pressure wave to SVC → rise ICP.
        ii. CVR factors:
            1. Autoregulation: allows flow-metabolism coupling
                a. Chemical - ↑ temp, ↓pO2 (<50mmHg), ↑pCO2 → vasodilatation → ↑ CBF → ↑ICP

   b. Neural – PNS activation → vasodilatation → ↑ CBF
   c. Drugs ↑CBF → ketamine, volatile anaesthetics

4. Position factors:
   a. Supine – usual ICP 5-15mmHg
   b. Erect – ↓ICP by the effects of gravity where CSF pools in spinal canal (↓22mmHg or 30cm H_20) in order to autoregulate CPP. This helps autoregulate CBF.
   c. Trendelenburg – head below the heart, so gravity causes CSF to pool in cranium → ↑ CSF volume → ↑ ICP.

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Physiol-00B6 Briefly discuss the physiological control of intraocular pressure.

1. Intraocular pressure is the pressure inside the globe of the eye
    a. Normal value = 10-20mmHg
    b. Diurnal variation ↑ night
    c. Measured by tonometers

2. The globe of the eye is a relatively non-compliant (non-elastic) container which contains 2 main fluids which can change in volume –
    a. Blood
    b. Aquaeous humour :
        i. Brings nutrients and removes wastes from the iris and lens
        ii. Controls IOP to maintain refractory index and appropriate curvature of cornea

3. Factors controlling intraocular pressure:
    a. Aquaeous humour: transparent acellular fluid which circulates in the anterior and posterior chambers of the eye. Low concentrations of protein, glucose and urea. Total volume = 3mLs.

        i. Production: produced from the ciliary body at 2-3 µ/min or 3mLs/day. Not regulated.
            1. Filtration of capillaries in the ciliary processes on anterior surface iris (33%)
            2. Active secretion by epithelial cells of ciliary process into the posterior chamber (66%), requiring carbonic anhydrase for HCO_3 production.
        ii. Drainage: resistance to this is the main controlling factor of IOP.
            1. Aquaeous humour secreted flows through the pupil into the anterior chamber, where it is absorbed by a trabecullar network → into the canal of Schlemm (thin walled vein) → venous plexus.
        iii. Control: normally production = drainage, where drainage is regulated according to IOP. ↑ IOP → ↑ pressure gradient for drainage.
        iv. ↓ drainage:
            1. Inflammation → debris obstruction of canal
            2. Venous obstruction
            3. Glaucoma (fibrosis of canal → narrowing)
            4. Mydriasis – closes angle between iris and trabecullar meshwork
        v. ↑ drainage:
            1. ↓ venous pressure → head up, ↓IT pressure (deep inspiration)
            2. Miosis → open angle
            3. Drugs: cholinomimetics
        vi. ↓production
            1. Beta-blockers, acetazolamide, mannitol

    b. Blood volume – same circulation as cerebral. Factor which ↑ blood volume:
        i. ↑ blood flow: ↑$PaCO_2$, ↑MAP (↑CPP), ↓PaO_2 (<50mmHg)
        ii. Drugs: suxamethonium, corticosteroids

    c. Extra-ocular factors – Extraocular muscle tone can influence globe compliance
        i. Blinking → ↑IOP 10-20mmHg

4. Consequences of ↑IOP (>20mmHg)

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a. Normal IOP maintains sufficient pressure to keep the eye distended
b. ↑↑ IOP (>25mmHg) causes:
    i. Compression of optic nerve axons → injury
    ii. Compression of optic vessel → ischaemic injury
    iii. Clinical blindness and corneal opacification

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Physiol-09B14 Outline the central nervous system effects on an awake person breathing air containing carbon dioxide.

1. Normal air inspired by humans contains negligible amounts of CO_2.

2. Effect of ↑ Inspired CO_2:
    a. Causes of ↑$FiCO_2$:
        i. Environment – severe pollution (closed space combustion, car exhaust)
        ii. Anaesthesia - CO2 absorber system dysfunction, inadequate tidal volumes to clear dead space air.
    b. ↑$PaCO_2$: ↓ concentration gradient for diffusion out of capillary → alveolus

3. Central nervous system effects:
    a. Metabolic cerebrovascular autoregulation:
        i. CO_2 causes direct cerebral vessel vasodilation → ↓ CVR → ↑ CBF (CBF = CPP/CVR) → ↑ICP (↑ pCO_2 1mmHg → ↑CBF 4%)
        ii. Consequences of ↑ICP: ↓CPP → direct stimulation of vasomotor centre → ↑ SNS → ↑ MAP

    b. Stimulation respiratory centre:
        i. ↑ $PaCO_2$ → ↑CO_2 diffusion across BBB into ECF → ↑HCO_3 + H^+ → ↓pH → stimulation of central chemoreceptors.
        ii. Central chemoreceptors → ↑ TV/RR → compensatory controlling of CO_2
        iii. ↑ pCO_2 1mmHg →↑MV 2L/min
        iv. The above response diminished by volatile anaesthetics, opioids, CNS depressants. Also, ↑MV will compound the problem as ↑↑inspired CO_2.

    c. Sympathetic stimulation:
        i. ↑CBF → ↑ICP → activation vasomotor centre
        ii. ↑circulating catecholamines → ↑ HR, ↑MAP, peripheral vasoconstriction, glandular activation
        iii. Clinically: cold, clammy and sweating, tremor and anxiety.

    d. CO_2 narcosis: direct CNS depression when pCO_2 > 100mmHg
        i. Confusion, agitation
        ii. Respiratory depression → coma → death

EXTRA-NOTES

4. Cardiovascular effects: warm, flushed, tachycardic with bounding pulse
    a. Indirect:
        i. SNS stimulation
        ii. Co-existent hypoxia
    b. Direct:
        i. Peripheral vasodilation
        ii. Direct myocardial depression
        iii. ↑ risk arrhythmias

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Physiol-05A10 Write brief notes on the physiological changes associated with sleep.

1. Sleep is a state of loss of consciousness where one can be aroused by sensory stimulation. The exact physiological mechanism of sleep remains unclear.

2. Sleep cycle – there are 2 phases of sleep: REM and non REM with unique system physiological characteristics. Typically:
    a. 90 min cycles: start phase I → IV
    b. 5-20min REM per 90 min
    c. As night progresses ↑ proportion REM sleep
    d. Generally predominance of PNS during sleep, less so in REM

System	REM sleep	Non REM Sleep (slow wave)
CNS	EEG: high frequency, desynchronised waveforms resembling wakeful EEG. Arousal threshold ↑ → paradoxical sleep as EEG suggests a more wakeful state Cycle: occurs for 5-20min/90min sleep, 4x per night Clinical: active dreaming, rotating REM $CMRO_2$ = awake	EEG: 4 stages – 1 – β/α waves replaced by θ waves (low amplitude, high frequency) 2 – bursts of sleep spindles (α-like waves) 3 – lower frequency, high amplitude δ waves with bursts of rapid waves (K-complexes on top) 4 – synchronised δ waves Clinical: Restful, dreams not remembered $CMRO_2$ = reduced
CVS	HR irregular BP variable	HR ↓10-30% BP ↓ in line due to ↓HR/SV (venous pooling)
Resp	RR irregular, variable TV/MV: ↓↓ 25% pCO_2: ↑ 3mmHg, ↓response hypercapnoea pO_2: ↓ 3mmHg, ↓response hypoxia AWR: ↑ FRC: ↓ (flat position, ↓ rib movement) Upper airway: ↓↓ tone → OSA	RR unchanged TV/MV: ↓ progressive through stages pCO_2: ↑ 3mmHg, ↓response hypercapnoea pO_2: ↓ 3mmHg, ↓response hypoxia Upper airway: ↓↓ tone → OSA
Muscle	↓↓ general muscle tone twitching with dreams Locus coeruleus → inhibition voluntary muscle activity	↓ muscle tone progressive through stages ↓ muscle tone,↑ venous pooling
Metabolic	BMR: ↓10-30% Temp: ↓0.5 Shivering: ↑ threshold	
Endocrine	ADH: ↑ → concentrated low volume urine Pituitary: GH, testosterone, PL, melatonin ↑	
GI	Motility ↑ (PNS tone)	Motility ↑ (PNS tone)
Other		

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93A1 Discuss the physiological consequences which you would expect to occur during the first few hours of a traumatic section of the spinal cord at the level of C6 assuming no other injuries.

1. The spinal cord carries important motor, somatosensory and autonomic pathways. A section of the lower cervical cord will affect all of these pathways.

2. Spinal shock: acute depression of spinal reflexes which return in approximately 2 weeks (and become hyper-reflexive).
    a. Unknown cause:
        i. ↓ reflexes: loss of tonic activation by descending pathways
        ii. ↑ reflexes: denervation hypersensitivity
    b. RMP 2-6mV higher than normal

Pathways	**Effect**
Motor Respiratory	Flaccid paralysis from C7 downwards → complete quadriplegia Diaphragm intact as phrenic n supplies diaphragm C3,4,5 Loss of thoracic, chest wall and intercostal muscles Diaphragm dependent breathing → ↓FRC, TV, FEV_1 → ↑RR
Sensory	Loss of sensation form C7 downwards: Lateral spinothalamic tract: carries pain and temperature Anterior spinothalamic tract: carries light touch, pinprick, itch Dorsal columns: vibration, proprioreception
Autonomic Cardiac Peripheral vascular Urogential GI Thermoregulation Endocrine	SNS – thoracolumbar T1-L2, PNS – sacral S2-4 Intact vagal tone (CN X) + severed SNS innervation → bradycardia, ↓contractility → ↓CO Loss normal SNS tone → vasodilation → ↓SVR → ↓MAP with no SNS compensation Severe hypotension requiring fluid resuscitation and vasopressors Loss PNS sphincter tone and erectile control → urinary retention, priapism Loss PNS pelvis innervation → constipation, faecal incontinence Vasodilation → ↑transfer core heat to periphery → ↑heat loss → hypothermia ↓ circulating catecholamines (↓SNS innervation of adrenal gland) ↓ catecholamine stimulation of RAS → exacerbates hypotension

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1993 Outline the neuroendocrine functions of the brain

1. The neuroendocrine functions of the brain are carried out by the hypothalamic-pituitary axis. The axis is divided into the:
    a. Anterior pituitary – hypothalamus regulates hormone release via release of vascular stimulating/inhibiting factors.
        i. Parvocellular neurons in hypothalamus → secrete hypophysiotrophic hormones → hypophysial portal system → anterior pituitary.
    b. Posterior pituitary – hypothalamus regulates hormone release via direct neural connections.

Hormone	**Hypothalamic factor**	**Control**	**Action**
ADH	Extension of hypothalamus. Hormone synthesised in cell bodies, transported down axon to hypothalamus and stored in vesicles.	Synthesised magnocellular cells hypothalamus (+) ↑ osm (supraoptic and PV nuclei, Na, mannitol), ↓ ECF volume (baroreceptors) , Ang II, stress, neurosurgery, pain, standing, drugs (opioids, barbiturates, carbamezapine) (-) alcohol	V_2: GPCR → ↑ cAMP → ↑expression aquaporin A_2 channels in CD → ↑ water reabsorption, concentrate urine V_1:GPCR → ↑IP_3/DAG → Vasoconstriction vessels, platelet aggregation
Oxytocin		Synthesised magnocellular cells hypothalamus (+) PNS (-) SNS, drugs (opioids, alcohol, β-agonists)	Contracts mammary gland → milk ejection Uterine contraction in labour
ACTH	(+) CRH (-) somatostatin	(+) stress, heat, toxins, catecholamines, vasopressin (-) glucocorticoids (negative feedback)	GPCR → cAMP linked receptor ↑ steroid synthesis ↑
GH	(+) GHRH (-) somatostatin	(+) starvation, ↓BSL, exercise, excitement, α-adrenergic, dopaminergic, amino acids (-) somatostatin	Tyrosine kinase linked receptor ↑ Normal growth with thyroxine, sex and adrenocortical hormones. ↑ protein synthesis, transport ↑ BSL → anti-insulin mobilises FFA → ketogenic Skeletal growth
LH	(+) GnRH (-) prolactin		Stimulates ovulation, luteinisation of ovarian follicles, testosterone secretion
FSH	(+) GnRH		Stimulates development ovarian follicles, regulates spermatogenesis.
PL	(+) PRH (-) somatostatin, dopamine	(+) suckling breast (-) tonic inhibition by dopamine	Development mammary glands, milk production Galactotransferase → ↑ fat, lactose in milk Supress LH → amenorrhoea

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TSH	(+) TRH (-) somatostatin	(+) cold in children (-) Negative feedback loop, dopamine, somatostatin, glucocorticoids, heat	GPCR → PLC → IP_3, DAG CNS development, mentation CVS catecholamine response, ↑ fluid resorption Bone development Metabolic: ↑ BMR, ↑ lipolysis, ↑ protein breakdown GI: ↑ carb reabsorption

Ho Medical ANAESTHESIA

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Make-up: Briefly describe the physiology of pain

1. Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.

2. Peripheral mechanisms
    a. Primary afferent nociceptors

Receptor	**Stimulus**	**Roles**
Na/Ca Ion channel	Mechanical, thermal chemical	Inward current of Na/Ca causes nociceptor depolarisation, when threshold > -50 mV. Sensitive to tetrotoxin block.
K ion channels		Hyperpolarise cell membrane and decrease nociceptor excitability.
VDCC (voltage dependent Ca channel)	As above	↑ intracellular Ca^{2+} in response to depolarisation → release substance P and CGRP
TRPV (vallinoid receptor channel)	Capsaicin, heat, acid, inflammation, ischaemia, endogenous lipids	
ASIC (acid sensitive ion channel)	Extracellular acid (inflammation)	
Purigenic		
$5HT_3$ ionotrophic	Serotonin	Released by platelets and enterochromaffin cells → activate Aδ and C fibres.

    b. Visceral afferents:
        i. ↓ density of nociceptors → dull poorly localised pain
        ii. Afferents converge along sympathetic and parasympathetic fibres → referred pain.
    c. Afferent nerve fibres:
        i. Aδ fibres:
            1. carry fast pain
            2. release glutamate at nerve ending
            3. terminate lamina I, V
        ii. C fibres:
            1. carry slow pain
            2. Release substance P, CGRP, VIP at nerve ending
            3. Terminate lamina II
    d. Peripheral sensitisation:
        i. Repeated injury/inflammation to an area → release of multiple chemicals (inflammatory soup) → ↑ sensitivity and hyperalgesia.
        ii. Opioid receptors synthesised in cell bodies can travel down to be expressed on peripheral nerve endings when tissue is inflamed.
        iii. Nerve injury:
            1. ↑ production of *ectopic discharges* near DRG
            2. Nerve GF (NGF) → *peripheral and central sensitisation* mediated by inflammatory mediator release.

3. Dorsal horn: site of termination of primary nociceptive afferents
    a. Entry via dorsal and ventral roots
    b. Second-order neurons:

i. Nociceptive-specific – located within superficial laminae and selectively respond to noxious stimuli
ii. Wide dynamic – located in deeper lamina (V) and respond to noxious and non-noxious stimulus. These neurons can become sensitised causing allodynia to a normal tactile stimulus.

c. Ligand– receptor interactions

Ligand	Receptor
Glutamate	NMDA, AMPA, kainite, glutamate metabotropic
Substance P	Neurokinin
Neurokinin A	Neurokinin
CGRP	
Endorphins	Opioid
GABA	GABA
serotonin	5HT

d. Central sensitisation (secondary hyperalgesia): ↑ responsiveness to normally innocuous stimuli in uninjured tissue surrounding the zone of inflammation. Due to several processes:
i. Windup: repeated stimulus from periphery → ↑ response from dorsal horn neurons mediated by release of excitatory neurotransmitters → activation of NMDA receptor → other neurons more sensitive to other peripheral input.
ii. Expansion in receptor field size
iii. ↑ magnitude and duration of response to stimuli
iv. ↓ threshold whereby normal stimuli are transmitted as nociception.
v. Long-term potentiation: strengthening of efficacy of synaptic transmission that occurs following activity across that synapse due to processes such as:
1. ↑Ca^{2+} influx
2. NO production → ↑ **NMDA receptor activation**
3. PKC generation

e. Spinal modulation:
i. Gate-control theory: afferent impulses arriving in dorsal horn cause local feedback inhibition through inhibitory interneurons which synapse between Aδ/C afferent and the substantia gelatinosa. The transmission from primary -> secondary neurons is gated by these interneurons.
Large diameter Aβ fibres activate inhibitory interneurons → ↓ transmission
Small diameter Aδ/C fibres inhibit inhibitory interneurons → ↑ transmission
ii. Specific receptors:
1. Opioid receptors: 75% presynaptic, 25% post-synaptic in dorsal horn → ↓ release of neurotransmitters from nociceptive primary afferents
2. α-adrenoreceptors: stimulation has analgesic effect with synergism with opioid.
3. GABA/Glycine: tonic inhibition of nociception. $GABA_A$ post-synaptics, whilst $GABA_B$ presynaptic.

4. Ascending tracts:
a. Spinal columns: Dorsal and ventral horn second order neurons cross the midline and ascend in the contralateral ventrolateral funiculus, making up the spinothalamic, spinoreticular and spinomesencephalic tracts. Some do NOT cross the midline and ascend ipsilaterally.
b. Supraspinal structures:

   i. Spinoreticular tract → brainstem nuclei (nucleus reticularis, nucleus subcoerulus, medullary raphe): activate descending modulation pathways, generalised arousal, motor reflexes.
   ii. Spinomesencephalic → superior colliculus, PAG: autonomic reflexes, integrated behavioural responses to pain.
   iii. Spinothalamic:
      1. Ventroposterior nuclei (lateral): sensory discrimination of pain, small receptive field, high threshold.
      2. Intralaminar nuclei (medial): affective-motivational response to pain, large receptive fields, low threshold.

c. Cortical:
   i. Somatosensory cortex: sensory-discriminative pain perception
   ii. Cingulate gyrus: affective pain perception

5. Descending modulation: inhibition of pain pathways occurs via
   a. Structures: PAG, hypothalamus, locus coeruleus, nucleus raphe magnus.
   b. Neurotransmitters: 5HT, NA, CCK, GABA, encephalin