NEUROPHYSIOLOGY AND PHARMACOLOGY

NEUROPHYSIOLOGY

Outline the basic electrophysiology of nerve conduction

Resting membrane potential

Outline the factors contributing to the generation and maintenance of the resting membrane potential: PAST QUESTION

Neural tissue (Neurons):
- 2 characteristic structural + functional features: excitable membrane, + synapses
- Excitability = ability of neurons to generate + propagate electrical impulses (AP)
- Synapses = specialised points of communication that allow neurons to communicate with each other

RMP
- The membrane potential of the cell = the electrical voltage of interior relative to exterior
- RMP = -70mV in nerve; -90mV in skeletal muscle cells

How is the membrane potential produced?

RMP is generated by uneven distribution of charged particles (i.e. ions and proteins) across the cell membrane 2o to:

1. **Semi permeable membrane / selective membrane permeability to different ions**
   - At rest CM is:
     - Slightly permeable to Na: Na channels closed
     - Very permeable to K: open K+ leak channels → K down conc gradient from ICP to ECF
     - Variable permeability to Cl based on cell type
2. **Different ionic concentrations of ICF and ECF**
   - Na+: 140mmol/L ECF; 20mmol/L ICF
   - K+: 150mmol/L ICF; 5mmol/L ECF
   - Na/K ATPase: 3Na+ out for 2K+ in. Consequences:
     - Osmotic effect: ↑ECF [Na+] balances osmotic effect of ↑intracellular conc of –vely charged protein
     - Electrogenic effect: cell interior hyperpolarised
3. **Gibbs Donnan effect**
   - Minor contribution to RMP
   - unequal distribution of large –vely charged protein impermeable to CM → affects distribution of other diffusible ions (K, Cl) and hence RMP by ~-10mV

Principles

1. **Nernst equation**
   - Nerst potential: voltage difference generated by EC gradient of an ion across CM (assuming complete permeability) i.e. contribution that a single ion makes to RMP
   - Calculated from valency, conc difference across membrane, and temp
   - The ion with ↑membrane permeability → Nerst potential has ↑contribution to total RMP
   - Nernst applied:
     - RMP has ↑K permeability → net efflux of +vely charged K down conc gradient → drives membrane potential towards Nernst potential for K+
     - RMP ↓permeability to Na+ ions
     - Therefore: measured neuronal RMP (-70mM) = close to Nernst potential for K+
2. **Goldman –Hodgkin-Katz equation**
   - considers all ionic permebailities and concentrations → RMP more precisely quantified
3. **Gibbs Donnan effect**

Key equation: the Goldman–Hodgkin–Katz equation

$$E_m = \frac{RT}{F}\ln\frac{P_K[K^+]_o + P_{Na}[Na^+]_o + P_{Cl}[Cl^-]_i}{P_K[K^+]_i + P_{Na}[Na^+]_i + P_{Cl}[Cl^-]_o}$$

where E_m (mV) is the calculated membrane potential and P_X is the permeability of the membrane to ion X.

Note:
- If the membrane is permeable only to K^+, then P_{Na} and P_{Cl} equal zero and the equation reduces to the Nernst equation for K^+.
- There is no valency term as only monovalent ions are considered.
- The concentrations of Cl^- are shown opposite to those of K^+ and Na^+ to account for its negative valency.

Typical RMPs of various cells

Cell type	RMP (mV)
Myelinated Axon	–70
Skeletal muscle	–90
Cardiac myocyte	–80
Cardiac pacemaker	nil fixed RMP (prepotential –60)
Smooth muscle	nil fixed RMP (–20 to –60)

Key equation: the Nernst equation

$$E_X = \frac{RT}{zF}\ln\frac{[X]_o}{[X]_i}$$

where E_X (mV) is the Nernst potential for a particular ion, R is the universal gas constant (8.314 J/(K mol)), T (K) is the absolute temperature, F is the Faraday constant, the electrical charge per mole of electrons (96 500 C/mol), z is the valency of the ion, $[X]_o$ (mmol/L) is the ion concentration outside the cell and $[X]_i$ (mmol/L) is the ion concentration inside the cell.

Action potential

General
- AP = electrical response of neurons and other excitable tissues during which membrane potential rapidly ↑ and ↓
- All or nothing phenomenon
- Allow rapid signalling within excitable cells over long distances
- AP results from brief ↑ in membrane conductance to Na+, followed by slower ↑in membrane conductance to K+
- Key parameters
  - RMP -70mV
  - Threshold potential -55mV
  - Peak potential (depolarisation) +20-40mV
  - Duration of AP 1-2ms

Physiological basis

RMP
- uneven distribution of charged particles (i.e. ions and proteins) across the cell membrane 2o to:
- maintained by:
  - Selective permeability of membrane to different ions
  - Different ionic concentrations of ICF and ECF
  - Gibbs donnan
- Principles
  - Nernst
  - Goldman Hodgkin Katz
  - Gibbs donnan

Events of an AP:

- **Phase 1 - threshold potential**: depolarisation stimulus reaches neuron → CM reaches -55mV → activation of voltage gated Na+ channels → Na+ influx > K+ efflux
- **Phase 2 – AP**: rapid influx of Na → further depolarisation → +ve feedback → rapid upstroke → drives membrane potential to Nernst potential for Na of ~+50mV → peak potential +30mV
- **Phase 3 - repolarisation**: AP never reaches theoretical max (+50mV) due to 2 events:
  - 1. Inactivation of voltage gated Na^+ channels → ↓membrane permeability to Na^+
  - 2. Delayed activation of voltage gated K^+ channels: ↑membrane K^+ permeability → K^+ efflux → membrane potential driven back towards Nernst for K^+ of ~-90mV
  - Membrane potential briefly more –ve than RMP = "after hyperpolarisation" - due to gradual closure of voltage-gated K^+ channels
- **Phase 4 – restoration of RMP**
  - -70mV maintained by: Na/K ATPase (EC gradient) + Na/K pump

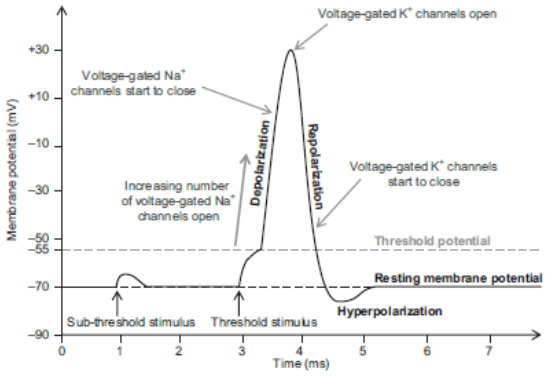


Figure 49.1 The nerve action potential.

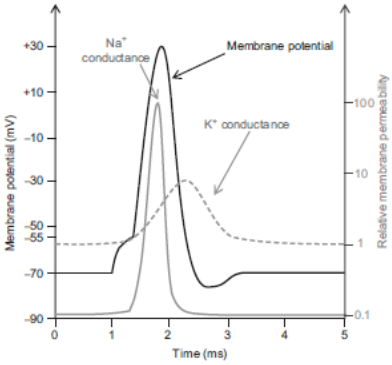
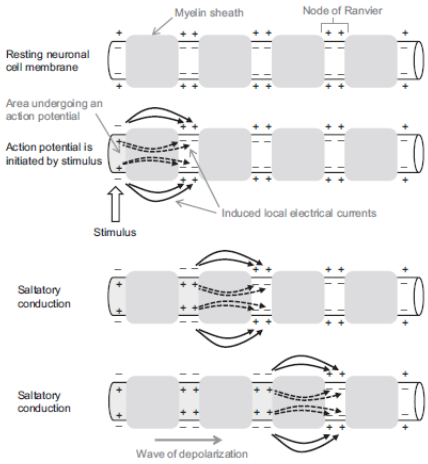


Figure 49.2 Changes in the membrane permeability of Na^+ and K^+ throughout the action potential.

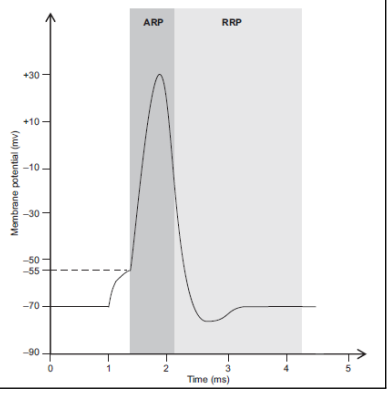
Conduction of nerve impulses: Saltatory conduction

- Electrical depolarisaiton propagates by formation of local circuits
  - Intracellular surface of resting portion of CM–vely charged
  - following AP → the portion of CM depolarises → intracellular surface +vely charged
  - ion movement at edges of the depolarised CM → current flow → neighbouring portions of C
- Velocity of conduction is dependent on several factors:
  - Axon diameter: ↑diameter → ↓resistance to flow → ↑conduction velocity
  - Transmembrane resistance:↑resistance → ↓loss of current flow → ↑conduction
  - Membrane capacitance: ↑capacitance → longer to alter polarity → ↓speed of propagation.
  - Temperature: ↑temp → ↑rate Na+ channel opening → ↑velocity
- Myelin
  - Produced by Schwann cells (PNS) + oligodendrocytes (CNS)
  - Nodes of Ranvier = exposed regions of membrane densely populated with voltage gated Na
  - Electrical impulse propagates across internode by local circuit conduction
  - Role:
    - Important determinant of nerve conduction velocity
    - Insulates axon: ↑transmembrane resistance; ↓loss of current to ECF
    - ↓effect of membrane capacitance
    - Saltatory conduction



Refractory period

- Time following an AP
- 1. ARP:
  - AP cannot be triggered whatever the size of the stimulus
  - starts from when voltage-gated Na+ channels open → continues until repolarisation 1/3 complete
- 2. RRP:
  - Repolarisation: K leak channels + voltage gated K channels open = K permeability is highest
  - AP only with ↑↑stimulus to counteract ↑K+ efflux
- Important for 2 reasons:
  - 1. Ensure unidirectional propagation of Aps
  - 2. Limiting frequency of APs



Synaptic function

Synapse = functional point of contact between 2 excitable cells, across which a signal can be transmitted.

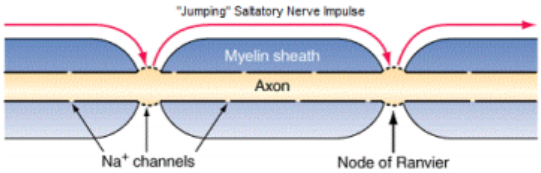
2 types of synapse:

- **1. Chemical synapse**
  - Signal relayed by chemical messenger (neurotransmitter)
  - Arrival of AP triggers NT release inot synaptic cleft → excites or inhibits post-synaptic cell
  - Unidirectional
  - Eg NMJ
- **2. Electrical synapse**
  - Pre + post synaptic cells are joined by gap junctions that allow electrical current to pass
  - AP in pre-synaptic cell induces local current in post-synaptic cell → triggers AP
  - Bidirectional
  - Eg cardiac muscle

What is salutatory conduction and what are the advantages of this type of conduction: PAST QUESTION

General

- Saltatory conduction: propagation of AP along myelinated axons, whereby wave of depolarisation "jumps" from one rode of Ranvier to the next
- Myelin
  - lipoprotein produced by oligodendrocytes (CNS) + Schwann cells (PNS)
  - myelin sheaths wrap around axons → interrupted at regular intervals (1-3mm) → exposing nodes of Ranvier
- Nodes of ranvier
  - Contain dense population of fast Na+ channels



Mechanism of saltatory conduction

- Depolarisation of a node → influx of Na ions → creating a sink (area of –ve charge at the surface)
- +ve charge on nodes ahead flows into sink → ↓polarity inside the membrane → AP → propagating current activates fast Na channels → wave of depolarisation down axon
- minimal electrical signal degradation as axon is insulated by myelin sheath
- AP reaches next node of Ranvier → continues down myelinated fibre
- Nerve impulses appear to rapidly jump from one node to the next

Advantages

- Faster
  - myelinated axons can propagate impulses over long distances at faster rate, without degradation of signal
  - conduction velocity of unmyelinated fibres = 2m/s vs. myelinated 200m/s
  - for a given fibre diameter → myelinated conduction velocity >> unmyelinated
- More energy efficient
  - Depolarisation largely localised to nodes of Ranvier → less ion flux required for conduction → ↓energy consumption by Na/K/ATPase to restore ion gradients → ↓energy required

Write notes on the axonal membrane: PAST QUESTION

Axon

- fibre like structure that leaves the cell body
- contains mitochrondria, microtubules, and SR
- terminals contain small vesicles packed with NT

Axonal membrane

- cell membrane which envelops the cytoplasm of an axon, separating cellular contents from ECF; bathed in ICF

Activation: saltatory conduction

- Electrical depolarisaiton propagates by formation of local circuits
- AP at one point in nerve axon sets up local electrical currents in adjacent resting membrane
  - Intracellular surface of resting portion of cell membrane–vely charged
  - AP → portion of CM depolarises → intracellular surface +vely charged
  - ion movement at edges of depolarised CM → current flow → depolarise adjacent membrane towards threshold → new AP fired
  - process continuous down axon + AP popagates form one end of nerve to other
- Velocity of conduction dependent on several factors:
  - Axon diameter: ↑diameter → ↓resistance to flow → ↑conduction velocity
  - Transmembrane resistance:↑resistance → ↓loss of current flow → ↑conduction
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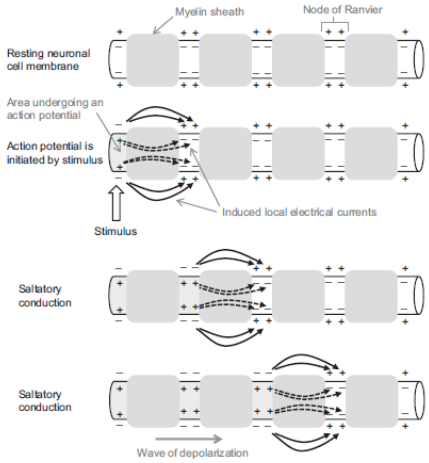


Types of axons

- 2 types of axons: unmyelinated and myelinated
- Myelin
  - Produced by Schwann cells (PNS) + oligodendrocytes (CNS)
  - Nodes of Ranvier = exposed regions of membrane densely populated with voltage gated Na channels
  - Electrical impulse propagates across internode by local circuit conduction
  - Role:
    - Important determinant of nerve conduction velocity
    - Insulates axon: ↑transmembrane resistance; ↓loss of current to ECF
    - ↓effect of membrane capacitance
    - Saltatory conduction

Explain the physiological mechanisms whereby an action potential arriving at a synapse might not be conducted: PAST QUESTION

Background

- AP = electrical response of neurons and other excitable tissues during which its membrane potential rapidly ↑and ↓
- Synapse
  - junction between a neuron and another cell (e.g. nerve, muscle) where a chemical (or electrical) signal is communicated
  - Consists of:
    - Presynaptic terminal: vesicles containing NTs → released by exocytosis in response to AP
    - Synaptic cleft: junction where NTs are released
    - Post synaptic membrane: contains receptors to which NT may bind → post synaptic stimulation

Reasons for non-conduction of AP

1. **Post synaptic refractoriness**
   - After post-synaptic membrane depolarisation → need repolarisation before being able to undergo another depolarisation

- 2 types:
  - ARP: post synaptic membrane unable to reach threshold irrespective of stimuli
  - RRP: need supramaximal stimuli to reach threshold

2. **Summation of EPSP not reaching threshold**
   - EPSP: partial depol in postsynaptic neuron → ↑excitability
   - Post synaptic membrane only depolarises when sum of EPSPs > threshold
   - Summation:
     - Spatial: activity from >1 synaptic knob facilitating another
     - Temporal: repeated stimuli producing new EPSP before previous EPSP decayed
   - If AP unable to generate combined EPSP > threshold → will not be propagated → failure of synaptic transmission
3. **Inhibitory post-synaptic potentials**
   - Inhibitory interneurons → ↑Cl channels → IPSP → post synaptic membrane hyperpolarisation → need greater summation of EPSP to reach threshold
4. **Presynaptic inhibition**
   - Axo-axonal synapses; GABA released → opens Cl channels, ↓amplitude of AP, or ↓excitatory transmitter release
5. **Presynaptic NT exhaustion**
   - Rapid repeated stimulation → deplete presynaptic NT + vesicles > rate of synthesis → synaptic fatigue → further APs unable to release NTs

NB summary of electrochemical events during synaptic transmission
(1) AP propagates down axon to presynaptic terminal
(2) Exocytosis of NTs
(3) NT diffuses across synaptic cleft + bind receptors on post-synaptic membrane
(4) Small depolarisation of post-synaptic membrane → excitatory post-synapticpotential (EPSP) → not enough to reach threshold
(5) Multiple EPSPs temporally + spatially summate to achieve threshold potential in post-synaptic membrane → propagation of signal

Describe the physiology of sleep

Sleep = necessary reversible ↓in conscious state from which one can be easily arousned by sensory or other stimuli

- Occurs in ~90min cycles
- **1. NREM (~80%):**
  - Slow wave sleep; deep restful sleep
  - Inhibition of midline pontine + medullar nuclei (raphe nuclei)
  - Characterised by: ↓HR, ↓PVR, ↓BP, ↓RR, ↓metabolic rate
  - 4 stages
    - Stage 1: drowsy (5%): α+ theta waves; hypnotic jerks
    - Stage 2: established (50%): spindles, K complexes; no consciousness
    - Stage 3: transitional (5%); delta waves
    - Stage 4: deep (15%): delta waves; difficult to wake; organised dreams
  - EEG: progression through stages → EEG more synchronised and slows
- **2. REM (20-25%)**
  - 5-20mins; at 90min intervals
  - Characterised by: random movements of the eyes, muscle atonia, vivid dreams
  - EEG: rapid low-voltage, irregular (desynchronised) activity
  - phasic characteristics intermittently

Sleep deprivation
- Altered cellular immune function
- ↓GH release
- cognitive impairment

Physiological changes that occur in sleep

	NREM	REM
CNS	active inhibition of RAS ↓discharge rate ↓CMRO2 ↑PNS activity	↑firing in limbic system + visual cortex PNS > SNS (tonic) SNS > PNS (phasic)
CVS	↓HR, CO, BP, PVR	Variable. Generally ↑HR, BP, vasoconstriction ↑muscle tone → ↑VR
Resp	↓TV by 10%; ↓FRC; ↓pharyngeal tone RR ↑or unchanged Slight hypoventilation → ↑PaCO2 + ↓PaO2	↓TV by 25% ↑RR + irregular ↓airway tone → worsens OSA atonia non diaphragm resp muscles
Renal	↓RBF → ↓GFR → ↑uterine concentration + ↓UO	As for NREM
GIT	↓saliva; ↑peristalsis	↓saliva; ↑peristalsis
Endocrine	↑GH secretion in stage 3+4 sleep ↑prolactin secretion; ↓cortisol	
Thermoregulation	Active thermoregulation to lower set point	Loss of thermoregulation

Outline the basis of the electroencephalogram

EEG
- recording of the electrical activity of the brain, measured using 19 scalp electrodes
- electrical portential generated by depolarisation of a single neuron = too small to be detected at scalp
- EEG records patterns representing synchronized depolarisation of groups of neurons
- electrical activity of the brain is categorized based on its frequency
  - delta waves: 0-4Hz
  - theta waves: 4-8Hz
  - alpha waves: 8-13Hz
  - beta waves: >13Hz
- Clinical uses of EEG:

- Diagnosis of epilepsy: seizure activity → organized, simultaneous activity in neurons
- Diagnosis of encephalopathy: progressive ↑in slow wave activity
- Adjunct test of brain death: isoelectric
- Measure of depth of anaestehsai
- Somatosensory evoked potentials (SSEPs)

Evoked potentials

EMG

Nerve conduction studies

Discuss the determinants and control of:

Intracranial and intraspinal pressure

- ICP = pressure within cranium exerted by a fixed vol consisting of:
  - Brain parenchyma: 80%
  - CSF: 10%
  - Cerebral blood vol: 5-8%
- Normal ICP: 5-15mmHg
- Monro-Kellie doctrine:
  - Skull is rigid continer of fixed volume that contains brain tissue, CSF, and blood
  - negligible elastance → any ↑in vol of one substance must be met with a ↓in vol of another or a ↑ICP
  - Once no further compensation can occur → ↑ICP exponentially → rapid decompensation → focal →global ischaemia
- Physiological response to ↑ICP
  - Displacement of CSF into spinal subarachnoid space
  - Compression of vascular bed
  - ↑CSF reabsorption

Determinants of ICP:

1. **Brain parenchyma:** i.e. tissue / water content
2. **CSF**
   a. Balance between formation + absorption
   b. Formation: choroid plexus + ependymal in ventricles; determined by CBF
   c. Absorption: arachnoid villi + cerebral venules; ↑linearly with ↑ICP up to 23mmHg; minimal absorption when ICP <7mmHg
3. **Cerebral blood volume**
   a. Sum of arterial + venous blood volumes
   b. Determined by CBF + drainage
   c. Couple with cerebral metabolic requirements for O2
   d. Autoregulated between MAP 50-150mmHg via myogenic response (Bayliss effect) – keeping CBF constant
      i. ↑by 2-4% for every mmHg↑PaCO2 (between 20-80mmHg)
      ii. ↑exponentially with PAO2 <50mmHg
      iii. ↑ with venous congestion
4. **Other** factors affecting CSF distribution and cerebral blood volume
   a. Posture
   b. ↑intrathoracic pressure → ↑CVP → ↑ICP

Regulation

- limited capacity due to rigid vault
- progressively ↑ ICP:
  - → CSF displaced into spinal and subarachnoid space + ↑ reabsorption by arachnoid villi and cerebral venules
  - → ↓CBV/ CBF → ischaemia → ↑SY outflow → ↑MAP → ↑CBF → ↑ICP
  - → herniation of brain parenchyma → coning → death

measurement of ICP

- 1. EVD: gold standard; catheter inserted ino lateral ventricle
- 2. Intraparenchymal probe: fibre-optic tipped catheter placed within the brain parenchyma through burr hole
- 3. Subarachnoid probe: obsolete
- 4. Subdural probe: obsolete

Physiological basis of treatment ↑ICP

- Can be classified as per the Monroe Kellie doctrine
- Brain
  - Osmotic agents e.g. mannitol, hypertonic saline → ↑plasma osmolality + expand blood vol → osmotic gradient between brain parenchyma and blood → ↓brain oedema + ICP
  - Evacuation of mass lesions + intracranial haemorrhage
- CSF
  - External ventricular drain → facilitates removal of CSF with a concominant ↓ICP
- Blood
  - Due to flow-metabolism coupling, ↓cerebral metabolic rate ↓O2 demans and therefore required blood flow
  - Drugs: Propofol, benzos, barbiturates → ↓cerebral metabolism → ↓O2 requirements and cerebral blood flow (also ↓seizure risk)
  - Hypothermia: ↓cerebral metabolism → ↓O2 requirements, CBF, and seizure risk
  - Prevention of hypoxia or hypocapnoea: both cause vasodilation → ↑CBV, CBF, and ICP
  - Induced hypocarbia causes vasoconstriction and subsequent ↓CBF and blood volume

Discuss the effects on ICP when a person is placed in a head down tilt: PAST QUESTION

General – see above

Effect of head down tilt on regulation of ICP

- trendelenberg ↑ICP via ↑cerebral blood vol
- healthy person will maintain normal ICP via compensatory mechanisms: CSF displaced into spinal subarachnoid space + ↑reabsorption via arachnoid villi and cerebral venules
- failure of compensatory mechanisms → eventually ↓CBF → ischaemia → cycle of ↑SNS → ↑MAP → ↑ICP
- avoid trendelenberg if concern re ↑ICP

Cerebral blood flow and autoregulation

- **CBF = CPP / CVR**
- CBF 15% resting CO → ~750ml/min or 50ml/100g brain tissue/min
  - CBF<50ml/100g/min → cellular acidosis
  - CBF<40ml/100g/min → impaired protein synthesis
  - CBF <30ml/100g/min → cellular oedema
  - CBF <20ml/100g/min → failure of cell membrane ion pumps, loss of transmembrane electrochemical gradients
  - CBF <10ml/100g/min → cell death

Determinants of CBF

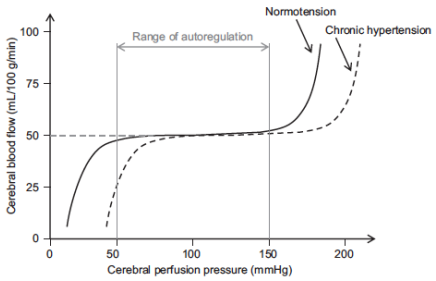
1. **CPP**
   - Net pressure gradient driving blood flow through the cerebral circulation
   - **CPP = MAP – ICP**
     - **MAP = CO x SVR;** CO = HR x SV; SVR = MAP / CO
     - ICP dependent on: brain, blood, CSF
2. **CVR**

Regulated by 4 primary factors

i. **Cerebral metabolism**
- flow-metabolism coupling: ↑metabolic demand → ↑CBF + substrate delivery
- Controlled by vasoactive metabolic mediators: H+ ions, K, CO2, adenosine, glycolytic intermediates, NO

ii. **CO2 and O2**
- CO2
  - At normotension: relationship between PaCO2 and CBF = almost linear
  - ↑PaCO2 → cerebral arteriolar vasodilation → ↓CVR + ↑CBF
  - ↓PaCO2 → cerebral arteriolar vasoconstriction → ↑CVR + ↓CBF
  - Initial stimulus = ↓brain ECF pH
  - Effects regulated by: NO, prostanoids, K channels, → ↓intracellular [Ca2+]
- PaO2:
  - little effect at normal PaO2
  - PaO2 <60mmHg → cerebral arteriolar vasodilation → ↑CBF
  - Mechanism: hypoxia acts on →
    - cerebral tissue to promote release of adenosine → cerebal vasodilation
    - cerebrovascular smooth muscle → hyperpolarisation → ↓Ca2+ uptake → vasodilation

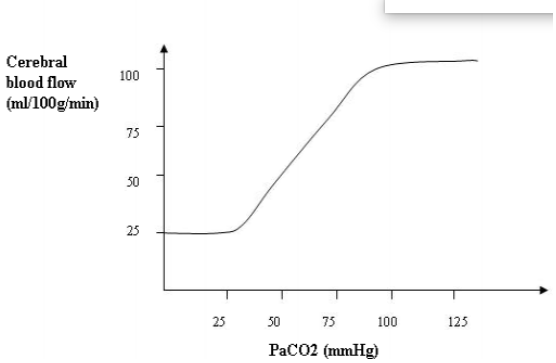
iii. **Autoregulation**
- Constant across CPP 50-150mmHg
  - CPP >150mmHg: CBF ∝ CPP
  - CPP <50mmHg: CBF <50ml/100g/brain tissue/min → ischaemia
- Stimulus to autoregulation = CPP (not MAP). Under normal circumstances (ICP
- autoregulation curve R shifted in HTN; L in neonates
- Mechanism:
  - Myogenic mechanism: arterioles vasoconstrict in response to ↑wall te ↑ or ↓CVR
  - May involve adenosine
  - Can be impaired in SAH, tumour, stroke, head injury



iv. **Neurohumeral factors**
- Relative lack of humoral + autonomic control on normal cerebrovascarul tone
- Main action of SY nerves = vasoconstriction

○ **Other factors**
- Blood viscosity: directly related to HCt; ↓viscosit → ↑CBF as per Hagen-Poiseuille law
- Temperature: ↓CMRO2 by 7% for each ↓1oC in temp
- Drugs
  - E.g. barbiturates ↓cerebral metabolism
  - Volatile agents → ↓tension cerebral vascular smooth muscle → vasodilation + ↑CBF

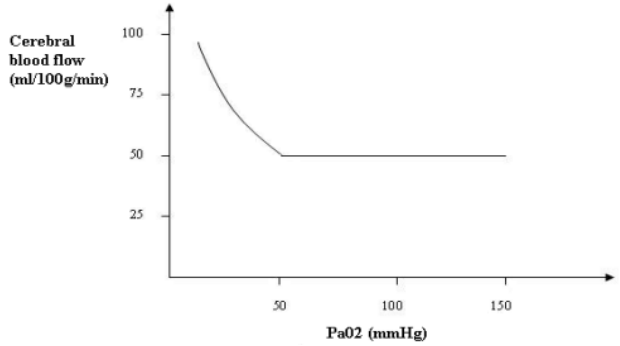
Measurment of cerebral blood flow:
- 1. Transcranial doppler USS: doppler to measure velocity of blood in middle cerebral artery → estimate CBF
- 2. Jugular bulb catheterisation: blood is sampled for O2 tension, Hb O2 saturation, and lactate → estimates adequacy of CBF
- 3. Kety-Schmidt technique: applies Fick principle; uses arterial + jugular venous [N2O] → global CBF
- 4. Radioactive xenon-133: radioactive decay of injected radioactive isotope ^{133}Xe detected by gamma camera → regional CBF
- 5. fMRI + PET: rely on flow-metabolism coupling to identify areas of ↑activity in the brain



Cerebral perfusion pressure

- perfusion of the brain is dependent on the pressure gradient between the arteries and the veins = CPP

- CPP = Net pressure gradient driving blood flow through the cerebral circulation
  - **CPP = MAP – ICP**
  - Normally 80mmHg
- Therefore CPP affected by anything that changes MAP or ICP
  - MAP = CO x SVR
    - CO = HR x SV
    - SVR = MAP / CO
  - ICP dependent on: brain, blood, CSF
    - Normal 5-15mmHg



Spinal cord perfusion

Arterial supply

- SC supplied by 3 arteries derived from post circulation of circle of Willis
- 1. One anterior spinal artery
  - Arises from branches of R + L vertebral artery
  - descends in anterior median sulcus
  - supplies anterior 2/3 of cord
- 2. Two posterior spinal arteries
  - Arise from posterior inferior cerebellar arteries
  - Descend along lateral aspect of spinal cord just medial to dorsal roots
  - Supply posterior 1/3 of cord
- Radicular branches arise segmentally from local arteries and supply local ares of cord
  - Most important = artery of Adamkiewicz at T8 and L1 (from anterior spinal artery)

Venous drainage

- 3 anterior + 3 posterior spinal veins located in pia mater → anastomose to form venous plexus → drains into epidural venous plexus

Spinal cord syndromes

Lesions to certain anatomical regions of the SC produce particular constellation of findings:

	Site of lesion	Symptoms/ signs
Complete transection	Complete transection through cord	- Loss of movement + sensation below the level of the lesion - Initially: paralysis flaccid → spastic - Bowel + bladder function lost - Lesions above T10 → impaired cough
Central cord syndrome		- Flaccid paralysis + loss of sensation of upper limbs > lower limbs
Anterior cord syndrome	Spares dorsal columns only	- motor function + pain + temp sensation affected below level of lesion
Brown-sequard syndrome	Hemisection of the cord	- ipsilateral loss of motor function below level of lesion - ilsilateral loss of light touch + proprioception below level - contralateral loss of pain + temp below level of lesion - ipsilateral loss of pain + temp at the level of the lesion
Cauda equina syndrome	Compression of lumbosacral nerve roots below level of cona medullaris	- can produce combination of UMN + LMN signs - radiculopathy, sacral sensory loss, asymmetric LMN weakness + atrophy, erectile dysfunction, urinary retention + overflow incontinence, constipation + overflow incontinence

Discuss the significance of the blood brain barrier

Blood brain barrier

- highly regulated interface that separates peripheral circulation + CNS

Structure

- **3 layers**
  - **capillary endothelial cells:** interconnected through tight junctions; (prevent free movement of solvent + solute); no fenestrations
  - **basement membrane:** endothelial cells + astrocytes (glial cells)
  - **astrocyte pedicles (foot processes):** ↓permeability of endothelial cells
- layers contain transporters (e.g. GLUT-1, ion channels/ pump) → controlled passage of specific electrolytes, nutrients, drugs
- layers contain enzymes (e.g. MAO, AChE) which degrade NTs → prevent passage across BBB

CNS structures outside BBB

- Sensing structures:
  - CTZ (area postrema): sensing noxious substances in peripheral circulation → trigger N+V
  - Hypothalamus: organum vasculosm laminae terminalis (OVLT) – contains osmoRs directly in contact with peripheral circulation → signal to release ADH in response to ↑osmolality
  - subfornical organ (SFO): contains osmoRs + glucose sensors → senses energy state of body
- Secreting structures:
  - Post. pituitary: releases ADH + oxytocin into circulation
  - pineal gland: regulates circadian rhythm via release of melatonin
  - choroid plexus
- NB CTZ, OVLT, SFO = circulventricular organs

Permeability

- **Permeable to:**
  - Diffusion:
    - Lipophilic substances: steroid homrones
    - Small molecules: e.g. CO2, O2, water
  - Facilitated diffusion:
    - movement of larger/ less soluble molecules down conc gradient
    - glucose (GLUT-1transporter)
    - hormones: insulin, thyroxine
  - Active transport:
    - small ions e.g. Na, Cl, K, Mg2+, Ca2+
- **Imperbeable to:**
  - Catecholamines: metabolised by MAO in cap endothelium → prevents their action as CNS NTs
  - Large proteins
  - Amino acids: prevent action as NTs
  - Ammonia: metabolised in astrocytes to glutamine → ↓neurotoxic effects

Function/ physiological significance

1. **Protection:**
   - From endogenous + exogenous toxins in plasma e.g. Br
2. **Immunological barrier**
   - Pathogens in blood (damaged BBB → encephalitis)
   - Body's immune system (autoimmune reactions)
3. **Maintain stable ionic environment in CNS**
   - Prevents free/ rapid diffusion of ions → optimizes neuronal function by preventing fluctuations in ions/ glucose
4. **Maintain stable pH**
   - Prevents rapid diffusion of H/OH- ions → stable CNS pH → important in regulation of respiration
   - CO2 freely diffuses across BBB → dissociates into H + HCO3 → alters CSF pH
   - Medullary resp centre uses CSF pH as surrogate marker for PaCO2
5. **Barrier for neurotransmitters**
   - Prevents leaking of NT out of CNS + prevents circulating NT from affecting CNS neural circuits

Situations of altered BBB function

- physiological: neonate (immature BBB)
- pathological: severe HTN, meningitis, seizure, ischaemic stroke, MS

Anaesthetic drugs that can cross BBB

- antimuscarinics: atropine penetrates BBB (tertiary amine), glycopyrolate does not (charged quaternary amine)
- D2 antagonists: metoclopramide penetrates BBB, domperidone does not

Describe the dynamics and metabolism of cerebrospinal fluid

- CSF = clear aqueous solution in ventricles + subarachnoid space; surrounds brain + SC
- Separated by blood via tight junctions between choroid plexus epithelial cells

Composition:

- similar to ECF; different from plasma
- compared to plasma, CSF:
  - [Na+] = same; 140mmolL
  - ↓ Ca2+ 1.2mmol/L; ↓K 3mmol/L; ↓glucose
  - ↓protein content so low acid-base buffering capacity
  - ↑PaCO2 (50mmHg) → ↓pH (7.33)
  - ↑Cl 120mmol/L, ↑Mg2+
  - Osmolality same (290mOsmol/kg H2O)

	CSF	Plasma
Sodium, Na^+ (mmol/L)	140	140
Glucose (mmol/L)	4	6
Chloride, Cl^- (mmol/L)	120	110
Bicarbonate, HCO_3^- (mmol/L)	24	24
pH	7.32	7.4
Protein (g/L)	0.2–0.4	70
White blood cells (cells/mm^3)	0–5	4000–11 000

Formation

- Normal = ~150ml; production: 500ml/day
- 2/3 by choroid plexus
  - fenestrated capillary endothelium (outside BBB)
  - ultrafiltration + secretion from stromal cells within choroid plexus
- 1/3 by extrachoroidal - Ependymal cells of walls of ventricles
  - 60% from oxidation of glucose

- 40% ultrafiltrate from cerebral capillaries
- Factors affecting CSF formation:
  - Rate of formation determined by **CBF** not ICP → therefore factors affecting CBF influence CSF production
  - CBF = CPP / CVR
  - ↑cerebral metabolic requirement for O2 → ↓choroidal blood flow
  - ↑intraventricular hydrostatic pressure >30cmH2O
  - ↑SY tone → ↓CBF
  - ↑PaCO2 → ↑CBF
  - ↓PaO2 → ↑CBF

Circulation

- choroidal plexus in lateral ventricles → 3rd ventricle via foramen of Munro → 4th ventricle via Aqueduct of Sylvius → cisterna magna via 2 lateral foramina of Lushka and Foramen of Magendie
- Passes either:
  - Cranially to basilar cisterns + via Sylvian fissure to cortical regions
  - Caudally to spinal subarachnoid space via central canal

Reabsorption

- 85% in arachnoid villi –in dural walls of sagittal + sigmoid sinuses; 15% spinal arachnoid villi
- reabsorption by pinocytosis + opening of ECF spaces
- pressure dependent: when CSF pressure 1.5mmHg > venous pressure

Functions:

1. **Mechanical protection of brain + spinal cord:**
   - ↓specific gravity → ↓effective weight of brain from 1400g to 47g
   - cushion for accelerating/decelerating injuries
2. **Pressure buffer**
   - role in Monro-Kellie doctrine → compensation for ↑BP or brain vol.
   - ↑ICP → ↑CSF absorption/ displacement into extracranial subarachnoid space → ↓ICP
3. **Acid base regulation (e.g. primary resp disorders) + control of respiration**
   - Medullary respiratory centre
   - Central chemoreceptors in floor of 4th ventricle + medulla; bathed in CSF → sensitive to Δ[H+]
   - CO2 diffuses into CSF → CO2 + H2O → carbonic acid → H^+ + HCO3 → H+ ions diffuse into chemoreceptor tissue → stimulate resp centre
   - Lower [protein] → ↓buffering capacity cf plasma
4. **Maintains constant ionic environment** → stable neuronal activity
5. **nutrition**: e.g. simple sugars, amino acids, O2 to brain
6. **waste removal**: excretion of toxic substances, metabolic by-products, CO2
7. other:
   - lymphatic function
   - neuropeptide transporter

Pathophysiology – hydrocephalus

- abnormal resistance to the circulation, or impaired absorption of CSF
- rate of CSF production > rate at which CSF can circulate past the obstruction or rate of absorption → local ↑CSF pressure within the ventricles → compresses brain parenchymal tissue → enlargement of ventricles (ventriculomegaly)
- ongoing compression of brain parenchyma → irreversible damage
- classified by site of obstruction to flow of CSF:
  - 1. No obstruction: overproduction likely pathology; choroid plexus papilloma
  - 2. Foramina of monro: e.g. compression by tumour
  - 3. Aqueduct of sylvius: e.g. congenital stenosis, tumor
  - 4. Outleets of 4th ventricle: e.g. SAH, chronic meningitis, congenital Arnold-Chiari malformation type II
  - 5. Arachnoid granulations: e.g. blood clots 2` SAH
- Management
  - External ventricular drain
  - Ventricular shunt: diverts CSF to peritoneal cavity or RA
  - Endoscopic 3rd ventriculostomy: allos CSF to pass directly into basal cisterns → bypasses obstruction in aqueduct of Sylvius or 4th ventricle

Describe cerebral and spinal cord metabolism including energy production, effects of temperature and factors leading to cell damage and cell death

- CBF = 15% resting CO
  - CBF = 5-ml/100g/min (20ml in white matter, 70ml in grey matter)
  - Reflects high O2 consumption of the brain → cerebral metabolic rate = CMRO2
  - CMRO2 is ↑in cortical grey matter

Energy production

- Brain + SC need ATP for enegy requiring processes e.g. ion pumps, synthesising proteins + lipid
  - Most ATP formation comes from aerobic metabolism (glucose)
  - major proportion generated by:
    - glycolysis (breakdown of glucose)
    - TCA: pathway that generates NAD- reduced form NADH and ATP
- Very limited capacity for anaerobic metabolism
  - Brain only able to witstand short periods of ischaemia as neurons produce ATP almost entirely by oxidative metabolism of substrates e.g. glucose, KB
  - In absence of O2, mitochrondria cannot convert NAD to NAD and lose energy of glucose oxidation
  - Without O2, energy dependent processes cease → irreversible cellular injury if blood flow not re-established rapidly
  - Anaerobic metabolism: if ↓↓↓ O2: Neurons die by apoptotic or necrotic mechanisms
    - Apoptosis = programmed cell death
    - Necrosis: when energy deprivation is more severe due to prolonged or extreme ischaemia → inflammation + damage to surrounding brain tissue

↓cerebral blood flow

- CBF <18ml/100g/min: irreversible neuronsal damage

-

Temperature: ↑temp → ↑cerebral metabolic rate → ↑cerebral O2 consumption

Describe the physiology of skeletal muscle including mechanism of excitation contraction coupling and compare the physiology of skeletal muscle with that of cardiac muscle

Compare and contrast a single twitch and a tetanic contraction in a skeletal muscle fibre. Include in your answer the physiological basis for the development of a tetanic contraction: PAST QUESTION

General

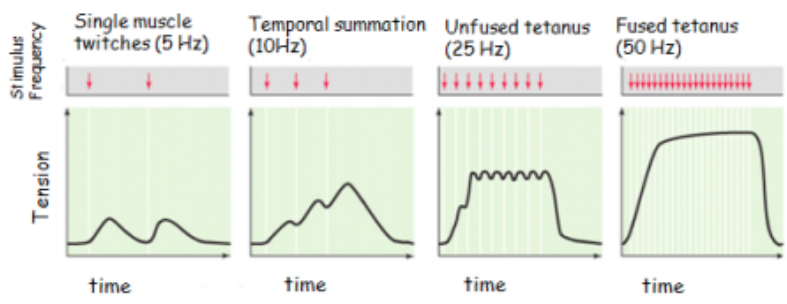
- skeletal muscle consists of muscle fibres which contract in response to electrical stimulation
- depending on nature of electrical stimuli → different mechanical repsonses i.e. single twitch vs. tetanic contraction
- muscle fibres contain:
  - multiple nuclei
  - myofibrils (actin + myosin) arranged in sarcomeres
  - cytoplasm → mitochrondria, T tubules, glycogen, myoglobulin

Single twitch contraction: Excitation-contraction coupling

- brief contraction of a motor unit e.g. in response to brief threshold stimulus followed by complete relaxation
- mechanism = EC coupling
  - motor neuron AP → arrives at NMJ
  - depolarisation of presynaptic membrane → release of ACh
  - ACh diffuses across NMJ → binds to postsynaptic nAChR on motor endplate
  - EPSP partial depolarise motor endplate → once temporal summation EPSP reaches threshold (-50mV) → muscle AP
  - AP propagates down muscle via T tubules → opens voltage gated L type (dihydropyridine) Ca2+ channels → stimulate SR ryanodine Rs → SR releases Ca2+
  - ↑intracellular [Ca2+] → binds troponin-tropomycin complex → unmasks myosin binding site on actin → cross bridges → contraction
  - muscle relaxes when ↓[Ca2+] → Ca2+ returns to SR (ATP dependent pump with Mg2+)

Tetanic contraction

- sustained maximal possible contraction of a motor unit e.g. in response to repeated high frequency threshold stimuli
- ARP and RRP of sleletal msucle very short → over before onset of relaxation
- Repetitive stimulation → summation of strength of mechanical contraction → tetanic contraction
- Mechanism: with each stimuli → ↑intracellular [Ca2+] → ↑cross bridges → ↑tension
- Tetanic contraction up to 4x tension of single twitch
- Consumes ↑energy than single twitch
- Critical frequency required for tetany
  - Depends on contraction-relaxation time of muscle fibre
  - Slow twitch fibres: contraction time 100ms → therefore require repeated stimuli >10Hz for tetanus
  - Fast twitch fibres: contraction time 10ms → therefore require repeated stimuli >100Hz for tetanus
- Offset of tetanus
  - Cessation of electrical stimuli → muscle AP stops
  - ATP depletion → muscle fatigue
  - Inhibitory effect from local lactic acidosis



Briefly describe the structure of mammalian skeletal muscle fibre and explain how its structure is related to its contractile function. DO NOT describe excitation-contraction coupling: PAST QUESTION

Background

- skeletal muscle fibres (myocytes) = specialised cells within muscle, arranged in parallel between tendinous ends

Structure	**Function**
Macroscopic	Additive force during contraction Movement of joints + stability for posture
- Muscle belly made of muscle fibres arranged in parallel - fibres innervated by motor neurons (Aα) - Each motor neuron can innervate multiple muscle fibres (motor unit)	

Microscopic	- Fibre:neuron ratio
	  - Fewer fibres to neurons → fine movement
	  - More fibres per neuron → gross movement
	- Prevents contraction without specific excitation (voluntary control)
	- Enables conduction of AP to SR
	- Stores and releases Ca2+ for EC coupling

- Muscle fibre comprised of: multiple nuclei, multiple myofibrils arranged in parallel, cytoplasm (sarcoplasm – mitochrondria, SR), conductive cell membrane (sarcolemma), T tubules, NMJ	
Molecular	Contraction via the sliding filament theory Isotonic: myosin binds to actin and bends → shortening fibres and keeping a
- myofibrils made of contractile proteins	

- Sarcomere = functional unit of myofibrils consisting of
  - Actin: thin, light protein, double strands
  - Myosin: thick, heavy protein, long tain, contractile heads
  - Troponin: globular protein with 3 subunits (I,C,T)
  - Tropomyosin: 2αhelical chains, prevents myosin-actin interaction

Muscle fibre types

- type 1 or slow twitch: ↑mitochrondria + myoglobin (red)
- type II or fast twitch: ↓mitochrondria + myoglobin (white); rich in glycogen

constant tension
Isometric: tension ↑ but muscle length is constant. Load = tension

Type I:

- responsible for posture
- fatigue resistant – moderate glycolytic activity, high oxidative capacity

Type II:

- responsible for fast movement e.g. running
- fatigues easily: high glycolytic activity but low oxidative capacity

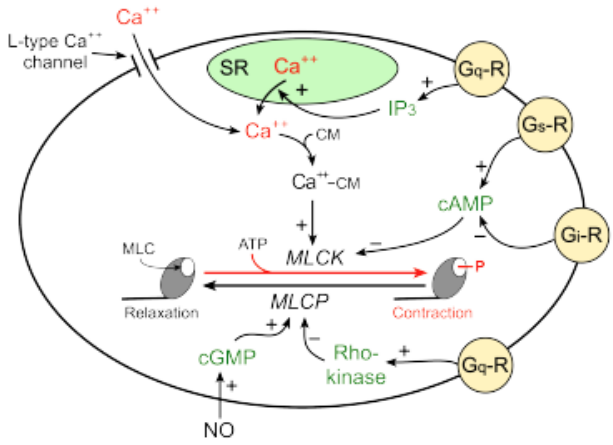
Describe the process of excitation-contraction within smooth muscle cells: PAST QUESTION

Smooth muscle: involuntary non-striated muscle

- locations
  - blood vessel tunica media + lymphatics
  - GIT
  - Resp tract
  - GUT: urinary bladder, uterus
  - Skin erector pili
  - Eye: ciliary muscle + iris
- Key features + differences from cardiac + skeletal muscle
  - Single nucleus
  - Not striated (irregular actin/myosin distribution)
  - No fixed tension-length relationship
  - Does not require nerve AP to stimulate contraction (automaticity)
  - Poorly developed SR → require extracellular Ca2+ for contraction
  - No troponin
  - Can maintain sustained contraction with minimal energy consumption (latched bridge mechanism)

Excitation contraction coupling of smooth muscle

- Excitation
  - Wandering (no fixed) RMP. Triggered by:
    - Spontaneous
    - ANS excitation (e.g. ACh binding mAChR)
    - Hormone/ autacoid control (e.g. NO, Ad, NAd)
    - Mechanical stretch
- Excitation contraction coupling
  - AP > threshold → opens L type voltage gated Ca2+ channels
  - Ca2+ influx → Ca2+ binds calmodulin
  - Ca2+-calmodulin complex activates MLCK (myosin light chain kinase) → phosphorylates myosin-ATPase → phosphorylates myosin + initiates myosin-actin cross bridge cycling → contraction
  - ↓intracellular [Ca2+] → dissociation of Ca2+-calmodulin complex → ↓activity of MLCK
  - MLCP (myosin light chain phosphatase) dephosphorylates myosin ATPase → uncoupling of actin-myosin cross bridge cycling
- Amount of actin-myosin cross-bridge cycling activity depends on balance of MLCK vs. MLCP activity –govered by intracellular [Ca2+]
- Latch bridge mechanism
  - sustained contraction despite ↓intracellular [Ca2+] + inactivated (dephosphorylated) myosin-ATPase → minimal energy consumption
  - I.e. actin-myosin cross bridge is latched in fixed contracted state



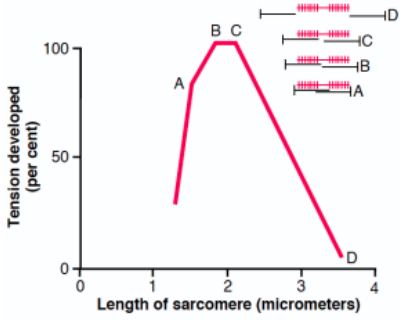
Describe the effect of resting muscle length and load conditions on the tension generated by a skeletal muscle. How do these factors affect the velocity of shortening: PAST QUESTION

Background

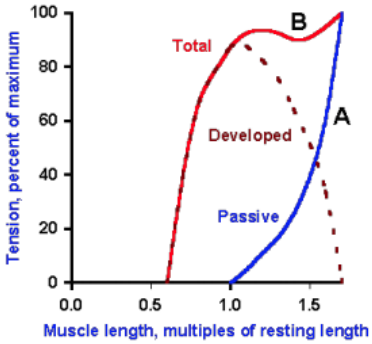
- basic functional unit of muscle fibre = sarcomere
- sarcomere: actin, myosin, troponin subunits, + tropomyosin
- tension developed 2 ways:
  - **active tension**: from actin-myosin cross-bridge cycling i.e. **sliding filament theory**…
    - describes the process how muscle fibres contract to generate active tension:
    - Muscle AP → opens voltate gated Ca2+ channels → stimulate Ca2+ release from SR → ↑intracellular [Ca2+]
    - Ca2+ forms complex with troponin C → releases tropomyosin from actin to expose myosin binding sites
    - Cross bridge cycling between myosin head + actin → actin pulled towards centre of sarcomere
    - ↓Intracellular (ca2+] via ATP dependent pumps
    - cross bridge cycling continue as long as intracellular [Ca2+] remains ↑
  - **passive tension**: from the elasticity of muscle and associated connective tissues (i.e. muscle + tendons will resist stretching)
  - **total tension = active tension + passive tension**

Length tension relationship

- Describes how active tension varies with fibre length
- As per sliding filament theory: amount of active tension generated ∝ number of cross bridges → ↑cross bridges → ↑tension
- Resting sarcomere length of skeletal muscle = 2.2um = optimal overlap between actin + myosin = ↑tension generated
- understretched → ↓myosin-actin overlap → ↓active tension
- overstretched → redundant actin-myosin overlap → ↓active tension

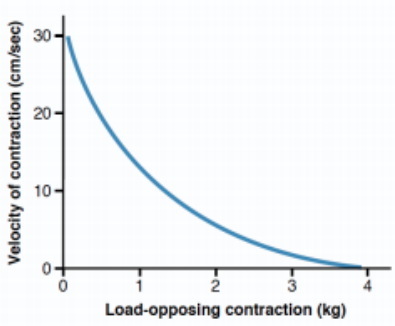


Load tension relationship

- describes how load influences total tension
- stretch of muscle prior to adding load → "passive" tension in muscle
- contraction of muscle creates active tension
- with ↑load → ↑muscle stretching → results in:
  - ↑passive tension
  - ↓actin-myosin overlap → ↓active tension that develops when muscle contracts
  - therefore total tension developed depends on balance between ↑passive tension and ↓active tension
  - 

Load velocity relationship

- Inversely ∝ to load on muscle
- Velocity maximal at resting length (for a given load)
- ↓velocity with ↑load
- when load = max tension able to be generated by muscle → no contraction results (i.e. contraction velocity = 0)



Neurophysiology – other

Outline the central nervous system effects on an awake person breathing air containing CO2: PAST QUESTION

General

- air usually contains negligible amount of CO2 (<0.04%)
- ↑PaCO2 can produce CO2 narcosis
- ↑FiCO2 occurs with:
  - severe air pollution (fire, car exhaust in enclosed space)
  - anaesthesia:
    - inadequate tidal volumes to clear dead space gas from lungs/ anaesthetic circuit in open circuit system
    - exhausted/ no CO2 absorber on anaesthetic machine in circle circuit system

Consequences of ↑FiCO2

- ↑FiCO2 → ↑PACO2
- Fick's law of diffusion: rate = A/T x C1-C0 s S/√ MW
  - Normally PACO2 < PVCO2 → CO2 diffuses down conc gradient from blood to alveoli → eliminated from body via lungs
  - ↑FiCO2 → ↓conc gradient between alveolus + pulmonary capillary blood → ↓diffusion CO2 out of blood into alveolus
  - if PACO2 > PvCO2 → conc gradient reversed → ↑uptake of CO2 into blood irrespective of MV → ↑PaCO2

CNS effects

- CNS
  - Cerebral blood flow
    - CBF = CPP/ CVR
    - Metabolic autoregulation: ↑PaCO2 → vasodilation → ↓CVR → ↑CBF (linearly by 2-4% for every 1mmHg ↑PaCO2 between 20-80mmHg)

- ↑CBF → ↑ICP (Monroe kellie doctrine)
- CO2 narcosis
  - PaCO2 >90mmHg
  - likely 2° alteration of intracellular pH → derangement of metabolic processes
  - Confusion, agitation, sedation, coma, death

- CVS
  - ↑PaCO2 → stimulates BS resp + autonomic centres → ↑SY outflow → ↑HR + ↑BP
- Resp
  - CO2 diffuses across BBB into CSF (H and HCO3 cannot cross BBB)
  - ↑$P_{CSF}CO2$ → ↓CSF pH by dissociating to H + HCO3
  - H stimulates chemoreceptors in brainstem resp centre → ↑firing receptor efferents → ↑RR ↑TV → **↑MV** → ↑pH

Describe the major sensory and motor pathways (including anatomy) - CICM

Spinal cord

- part of CNS
- begins superiorly at foramen magnum as continuation of medulla
- terminates at L1 or L2 → forms cona medullaris → filum terminale (pia mater) extends inferiorly + attaches to coccyx
- situated in vertebral canal
- surrounded by meninges, dura, arachnoid, pia mater
- bathed in CSF; occupies subarachnoid space + stabilised within dura by denticulate ligaments
- Transverse section:
  - Central: grey matter = neuronal cell bodies + synapses
  - Peripheral: white matter = myelinated ascending (sensory) + descending (motor) pathways
- 31 pairs of spinal nerves with dorsal + ventral roots

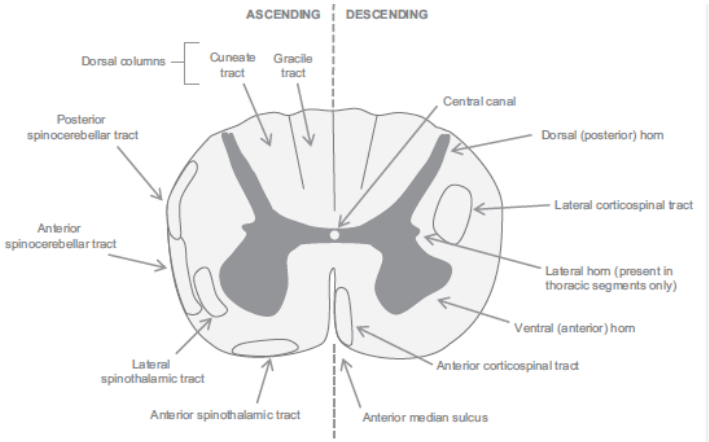


Figure 47.1 Cross-section of the spinal cord (extrapyramidal tracts not shown).

Ascending tracts (sensory)	Descending tracts (motor)
Convey sensory info from peripheral sensors to higher centres in brain. From posterior to anterior: 1. Dorsal (posterior) column: ○ fine touch + proprioception + vibration ○ crosses at the brain stem 2. Spinocerebellar tracts (ant + post): ○ Carry proprioceptive info from muscles + joints to cerebellum ○ Does not cross 3. Lateral spinothalamic tracts ○ pain + temperature ○ Crosses within 2 vertebral segments 4. Anterior spinothalamic tracts ○ crude touch + pressure ○ Crosses within 2 vertebral segments	Carry motor information 1. Corticospinal tracts (ant + lateral) "pyramidal tracts": ○ motor function – carry axons of UMN ○ crosses at the brain stem ○ Relay to alpha-motor neurons (LMN) in ventral horn of spinal cord 2. Extrapyramidal tracts: ○ rubrospinal, tectospinal, vestibulospinal, olivospinal, reticulospinal ○ Originate in brainstem nuclei and do not pass through medullary pyramids ○ Role in control of posture + muscle tone

Main sensory afferent pathways

2 major pathways by which sensory info ascends in the SC

- **1. Dorsal column-medial lemniscal (DCML) pathway**
  - carries sensory info about 2 point discrimination, vibration, proprioception
  - sensory signals pass through the dorsal columns of spinal cord, and medial lemniscus in brainstem
  - in spinal cord: 1st order neuron: long; enters + ascend in dorsal columns ipsilaterally
    - lower body: medial gracile tract → synapse gracile nucleus in medulla oblongata
    - upper body: lateral cuneate tract → cuneate nucleus
  - in medulla: 1st order neurons synapse with 2nd order → cross CL → ascend to thalamus (sensory decussation) → ascend to brainstem = medial lemniscus tract
- **2. Spinothalamic tract**
  - carries sensory info about crude touch + pressure + temp + pain
  - crosses midline at level of spinal cord
  - 1st order neurons: enter dorsal root SC → ascend or descend 1-2 levels along Lissauer's tract → synapse with 2nd order neurons in dorsal horn
  - axons of 2nd order neurons decussate anterior to central canal of SC in anterior commissure → ascend to thalamus in CL spinothalamic tract

Main motor efferent pathways

- **1. Corticospinal tract**
  - Primary route for somatic motor neurons
  - Composed of:
    1. Motor cortex: pre-central gyrus; results in initiation of movement
    2. UMN: originates in motor cortex → descends through SC within corticospinal tract
       - Travel through post limb of internal capsule
       - At pons: synapse in pontine nuclei → ventral part of pons → post-synaptic fibres travel posteriorly to cerebellum through middle cerebral peduncle
       - At medullary pyramids: 90% nerve fibres decussate → descend in lateral corticospinal tract of SC
       - 10% of nerve fibres that don't decussate descends in separate IL tract (anterior corticospinal tract)
       - UMN synapse with LMN in ventral horn of SC
    3. LMN
       - 1. α motor neurons: leave ant horn → form spinal nerve → exits spinal canal via intervertebral foramen → becomes peripheral nerve → innevates extrafusal fibres of skeletal muscle causing contraction

- 2. Gamma motor neuron: innervate muscle spindles; involved in proprioception

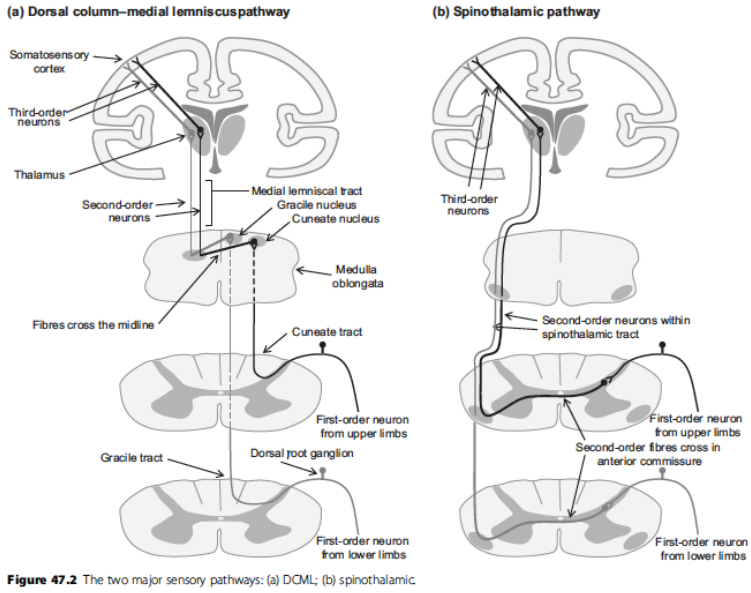


Figure 47.2 The two major sensory pathways: (a) DCML; (b) spinothalamic.

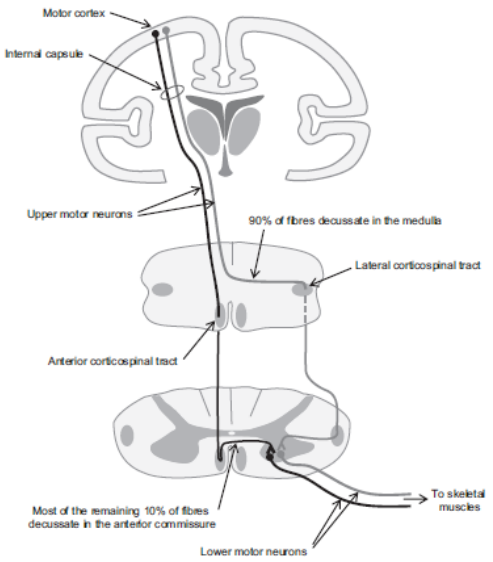


Figure 47.3 The corticospinal tract.

Arterial supply

- SC supplied by 3 arteries derived from post circulation of circle of Willis
- 1. One anterior spinal artery
  - Arises from branches of R + L vertebral artery
  - descends in anterior median sulcus
  - supplies anterior 2/3 of cord
- 2. Two posterior spinal arteries
  - Arise from posterior inferior cerebellar arteries
  - Descend along lateral aspect of spinal cord just medial to dorsal roots
  - Supply posterior 1/3 of cord
- Radicular branches arise segmentally from local arteries and supply local ares of cord
  - Most important = artery of Adamkiewicz at T8 and L1 (from anterior spinal artery)

Venous drainage

- 3 anterior + 3 posterior spinal veins located in pia mater → anastomose to form venous plexus → drains into epidural venous plexus

Spinal cord syndromes

Lesions to certain anatomical regions of the SC produce particular constellation of findings:

	Site of lesion	**Symptoms/ signs**
Complete transection	Complete transection through cord	- Loss of movement + sensation below the level of the lesion - Initially: paralysis flaccid → spastic - Bowel + bladder function lost - Lesions above T10 → impaired cough
Central cord syndrome		- Flaccid paralysis + loss of sensation of upper limbs > lower limbs
Anterior cord syndrome	Spares dorsal columns only	- motor function + pain + temp sensation affected below level of lesion
Brown-sequard syndrome	Hemisection of the cord	- ipsilateral loss of motor function below level of lesion - ilsilateral loss of light touch + proprioception below level - contralateral loss of pain + temp below level of lesion - ipsilateral loss of pain + temp at the level of the lesion
Cauda equina syndrome	Compression of lumbosacral nerve roots below level of cona medullaris	- can produce combination of UMN + LMN signs - radiculopathy, sacral sensory loss, asymmetric LMN weakness + atrophy, erectile dysfunction, urinary retention + overflow incontinence, constipation + overflow incontinence

Somatosensory nervous system consist of:

- Sensory receptors
  - Encode stimuli by repetitive firing of action potentials
  - E.g. proprioceptors, nociceptors, thermoreceptors, mechanoreceptors
  - Perception of stimulus dependent upon neuronal pathway rather than sensory receptor itself
  - 1st order neurons: transmit APs from sensory receptors to SC → synapse with 2nd order neurons → conduct AP to thalamus + synapse with 3rd order neurons → relay AP to cerebral cortex via internal capsule
  - Primary somatosensory cortex receives + performs processing of sensory info

Nervous system divided into:

- 1. CNS
  - Brain + spinal cord
  - Brain = site of higher integration of sensory inputs, motour putput, thinking + learning
  - Spinal cord = contains long sensory + motor pathways that convey information between the peripheray and the CNS
- 2. PNS
  - cell types are:
    - Sensory (afferent) neurons: relay info from external environment + viscera to CNS
    - Motor (efferent) neurons/ "somatic motor neurons": under voluntary control; transmit AP from CNS to skeletal muscle
    - Enteric neurons

- Autonomic neurons: SYNS + PSY

Classification of acute spinal cord injury

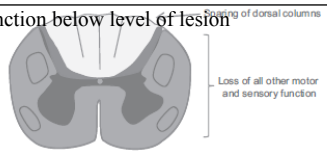
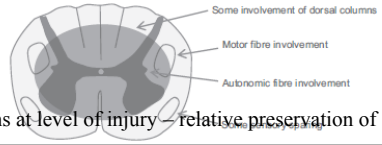
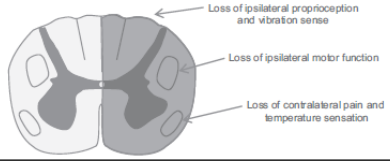
- Stability of vertebrla volumn
- Extent of neurological injury
- Level of injury:

Common patterns of injury

1. Complete spinal cord injury

	Level	Effect
Respiratory	Above T8	- intercostal muscle weakness/ paralysis → diaphragmatic contraction sole mechanism of inspiration → ↓FRC
	Below C5	- does not directly affect diaphragmatic contraction; - diaphragmatic contraction **indirectly** affected as a result of intercostal muscle paralysis → paradoxical movement of the chest wall → ↓VC by 50%
	C3 and above	- paralysis of all resp muscles → gross ventilator impairment with immediate ventilator support requirement
	Other effects	- Paralysis of external intercostals + abdo muscles → markedly ↓forced exp gas flows: ↓FEV1 + impaired cough - Impaired inspiration → basal atelectasis, ↓lung compliance, V/Q mismatch - ↓lung vol → ↓pulmonary surfactant production → ↓compliance + ↑WOB
Cardiovascular	Above T6	- Hypotension → neurogenic shock - SY outflow to systemic arterioles interrupted → arterial vasodilation - Venodilation → ↑risk thromboembolic disease, ↓VR → hypotension
	Above T1	- Bradycardia due to disconnection of SY cardioacceleratory nerves → unopposed bradycardia
PNS		- Disruption of motor, sensory, and autonomic fibres - initially: flaccid paralysis + loss of reflexes below level of SC lesion = spinal shock - over next 3 weeks → spastic paralysis + brisk reflexes develop - below level of injury: somatic + visceral sensation is absent
GIT		- Delayed gastric emptying + paralytic ileus - High spinal cord lesions: gastric ulceration (due to unopposed VA stimulation of GA secretion)
Metabolic		- Thermoregulation impaired due to loss of SY outflow below level of injury - Arteriolar vasodilation in skin → heat loss - Hyperglycaemia common due to stress response

2. Incomplete spinal cord injury

Level	Effect
Anterior spinal artery syndrome	- Paraplegia + loss of pain + temp sensation + autonomic dysfunction below level of lesion - Proprioception + vibration sensation intact 
Central cord syndrome	- Most common incomplete spinal cord injury - Results from hyperextension of the neck - Upper + lower limb weakness below level of lesion - Varying degree of sensory loss - Autonomic disturbance common esp bladder dysfunctic - Due to: selective axonal disruption of the lateral columns at level of injury – relative preservation of grey matter 
Brown sequard syndrome	3 characteristic clinical features: - IL motor weakness - IL loss of 2 point discrimination (fine touch) - CL loss of pain + temp sensation below level of lesion 
Cauda equina syndrome	- Lesion below L2 → compresses nerve roots rather than SC - Nerve roots carry sensory afferent nerves, PSY nerves + LMNs - Severe leg weakness, partially preserved sensation – saddle anaesthesia most common - Autonomic disturbance extremely common – urinary retention almost universal - Most common cause = acute central intervertebral disc herniation

Discuss the physiological consequences 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: PAST QUESTION

SC = part of CNS which contains tracts that relay motor, sensory, autonomic ino between enrve roots + higher centres

Acute traumatic section at C6 will result in:

- **Spinal shock**
  - Occurs immediately afer SC injury
  - Acute depression of spinal reflexes
  - Reflexes return after hours to weeks → hyperreflexia
  - Settles after swelling + oedema settle
  - Initially observed level of neurological deficit may be higher than level of injury due to cord oedema

Phase	Time	Finding	Underlying physiological event
1	0-1/7	Areflexia + hyporeflexia	Loss of descending facilitation
2	1-3/7	Initial reflex return	Denervation supersensitivity
3	1-4/52	Hyperreflexia	Xon supported synapse growth
4	1-12/12	Hyperreflexia + spacticity	Soma supported synapse growth

- **Disruption of all ascending + descending tracts below C6**

Pathway	Effect

Motor – corticospinal tract	Flaccid paralysis below C6 → tetraplegia Myotomes: C5 shoulder abduction preserved; C6 elbow flexion lost Flaccid paralysis of abdo muscles → weak cough → ↑aspiration risk
Resp	Diaphragm motor intact (phrenic via C3,4,5) but loss of motor innervation to intercostal + chest wall muscles → diaphragmatic breathing (↓depth ↑RR)
Sensory – dorsal columns	Loss of sensation, vibration, proprioception below C7
Pain – anterior + lateral spinothalamic tracts	Loss of pain, temp, pinprick, itch below C7
Autonomic – SY chain	Loss of SNS tone → vasodilation + venodilation → ↓SVR ↓preload → ↓MAP
Thermoregulation	↓SNS tone → vasodilation + venodilation → loss of thermoregulation → hypothermia
Cardia – SY chain, cardioaccelerator fibre	Loss of cardiac SNS inervation with intact VA nerves → profound bradycardia + ↓inotropy → ↓↓CO
GIT	Loss of PSNS innervation → constipation + faecal incontinence
Urogenital	Loss of sphincter + erectile control → urinary retention + priapism
Adrenal	↓SNS innervation to adrenal gland → ↓circulating catecholamines

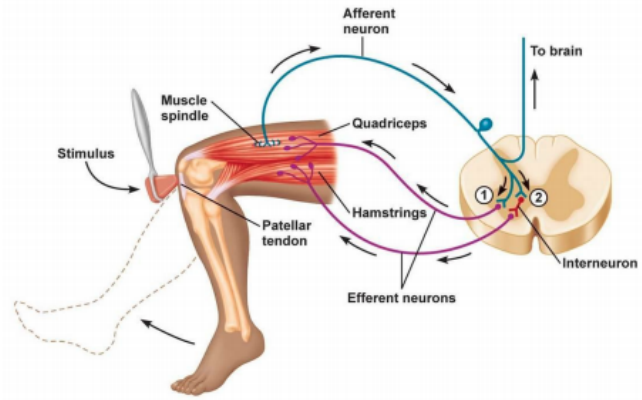
Describe the reflex arc

General

- Reflex = pathway involving nervous system resulting in predictable, repetitive response to sensory input; generally not involving voluntary control
- Knee jerk = monosynaptic spinal cord reflex
- pathway consists of:
  - sense organ
  - afferent neurone
  - one or more synapses
  - efferent neurone e.g. lower motor neurone: innervates muscle spindles
  - effector
- Classified by number of synapses involved: monosynaptic/ polysynaptic

Knee jerk

- monosynaptic reflex
- sense organ = muscle spindle in quadriceps
- output = reflex contraction of quadriceps → knee extension
- Mechanism
  - Patellar tap → quadriceps stretch → muscle spindles (bags + chains) stimulated → AP propagates via 1a afferents→ impulse to ventral horn of SC → direct synapse with αmotor neurone → excitation of extra-fusal muscle fibres → contraction of quads
  - excitatory NT: glutamate → EPSP → summation generates motor neurone AP
- reciprocal innervation:
  - synapse with inhibitory interneuron of opposing muscle group to allow relaxation; via glycine → IPSP
  - inhibition of antagonistic muscles i.e. hamstring knee flexors.



Muscle spindles

- Sensory receptors within muscle belly that detect: muscle length; rate of change of muscle length → involved in reflex control of msucle length
- Consist of specialised muscle fibres enclosed within a connective tissue capsule arranged in parallel with the muscle belly
- Contractile ends (y innervation), non contractile centre (Ia and II innervation) and 3-10mm in length
- Muscle spindles = intrafusal fibres
- Muscle belly = extrafusal fibres
- 2 types of muscle spindles
  - nuclear bag fibres
    - dynamic bag, fibres, and static bag fibres – characterised by centrally aggregated n
    - innervated by Ia primary afferents and y-efferents therefore sensitive to degree + rate of stretch (mainly Ia)
  - nuclear chain fibres
    - characterised by linearly arranged nuclei
    - innervated by Ia primary afferents, II secondary afferents and y-efferents therefore sensitive to degree of stretch (mainly II)
- Innervation
  - Ia afferent: sensitive to changing fibre length – dynamic
  - II afferent: sensitive to absolute fibre length – static
- Responses
  - Stretch of muscle spindle causes:
    - Reflex excites associated motor neuron → muscle contraction
    - Reflex inhibits antagonist motor neuron → relaxation of antagonist muscle
  - Slow stretch → ↑Ia and ↑II activity → static response
  - Sudden stretch → ↑↑↑Ia and ↑II activity → dynamic response

- Resulting contraction ↓tension on muscle spindles → completes reflex circuit
- Gamma Loop γ motor neurones serve 2 functions: (1) contract ends of muscle spindles ! stretches centre of nuclear bag spindles (2) maintain spindle sensitivity during stretch/contraction γ motor neurones are generally under the control of extrapyramidal system Example of gamma loop is the Jendrassik manoeuvre, whereby pulling own fingers leads to reinforcement of the knee jerk reflex

Describe the spinal reflexes: MAKEUP

Background

- Spinal reflex = stereotyped motor response to a specific sensory stimulus, without cortical involvement
- Function:
  - Protective: i.e. overstretching, painful stimuli
  - Balance: cross extensor

Types

- **Myotatic reflex**
  - Stimulus = rapid muscle stretch e.g. patella tendon vs. tendon hammer
  - Response = stretched muscle contracts rapidly e.g. knee jerk
  - Circuit: muscle stretch → muscle spindles excited → signal via Ia and II afferent sensory neurones → synapse at SC → msucle contraction (+relaxation of antagonist muscles)
  - Function: posture + counter sudden loads
- **Withdrawal reflex**
  - Stimulus = pain
  - Response = rapid limb withdrawal
  - Circuit: painful stimulus → cutaneous nociceptors excited → signal via pain fibres (e.g. Adelta) → synapse at SC → muscle contraction (+ relaxation of antagonist muscle)
  - Function = protect limb from noxious stimuli
- **Cross extensor reflex**
  - Stimulus = painful stimulus e.g. step on nail
  - Response = rapid extensor contraction + flexor relaxation in CL limb
  - Circuit = same as withdrawal reflex except interneuron decussates + activates CL motor neurons
  - Function = CL limb strengthens to balance body + prevent falling voer
- **Golgi tendon reflex**
  - Stimulus = forceful stretch
  - Response = relaxation of overstretched muscle
  - Cirtuit: forceful muscle contraction → tension applied to tendon ↑s → golgi tendon organ stimulated → signal via afferent Ib neurons → synapse at SC → inhibitor interneuron → hyperpolarises α motor neuron → muscle relaxation
  - Function = relaxes overstretched muscle before forces become to great as to result in tendon rupture

Describe the physiological control of intraocular pressure: PAST QUESTION

IOP = fluid pressure inside the globe of the eye; normal 10-20mmHg

Factors governing IOP

- aqueous humour volume
  - 2/3 produced by eye ciliary body in post chamber via active secretion involving CA
  - 1/3 via filtration from the anterior surface of the iris
  - absorbed via trabecular meshwork (Fontana's spaces) and into canal of Schlemm → drains into the episcleral venous system
  - Normal vol = 0.3ml; production = 3mls/day
  - ↑aqueous humour vol = ↑IOP by obstruction to drainage (e.g. mydriasis); ECF hypertonicity
- Choroidal blood vol → ↑IOP via:
  - ↑MAP
  - ↑PaCO2 → vasodilation
  - sig ↓PaO2 → vasodilation
  - ↑venous pressure from position, coughing, straining
- ↑external pressure → ↑IOP via:
  - extraocular muscle tone
  - external globe pressure
- pharmacological
  - mydriatic agents (sux, N2O) → ↑IOP
  - miosis agents: (carbonic anhydrase inhibitors, GA, volatiles) → ↓IOP

Consequences of ↑IOP

- globe has low compliance → small ↑vol → ↑↑pressure → nerve damage/ ischaemic injury

Describe the alterations to the physiology of the nervous system in the older patient and outline the consequent effects on pain perception: PAST QUESTION

Background

- pain = unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage
- ageing: age-dependent decline in physiological and cognitive reserve, which results in the progressive ↑in mortality rate of an individual

Alterations of ageing on the nervous system + effects on pain → 3 components

1. **CNS alterations**
   - Altered sensory + emotional perception of pain → ↑pain tolerance
   - Potential inability to voice pain despite perceiving pain
   - Potential inability to react to pain appropriately
   - Mechanisms:
     - Neuronal atrophy: ageing → ↓neuronal mass → cognitive decline + slower reflexes
       - Compensation:
         - **Redundancy**: more neurons than required for normal cognition
         - **Neuroplasticity**: more connections formed between remaining neurons
         - **Neurogenesis**: production of new neurons (e.g. hippocampus, basal ganglia)
     - ↓endogenous descending inhibitory pain pathways esp. opioids

        - ↓CBF
2. **PNS alterations**
    - Neuronal atrophy → ↓myelinted + unmyelinated axons + ↓number of synapses
    - Slower transduction + transmission of painful stimuli to CNS: ↓NT of primary afferent nociceptive fibres: substance P, and CGRP
3. **ANS alterations**
    - ↑circulating NAd but ↓response to catecholamines → ↓SNS tone → ↓SNS response (↑HR ↑BP) to painful stimuli

Outline the neuroendocrine functions of the brain: PAST QUESTION

- neuroendocrine function = interaction between nervous and endocrine systems
- brain exerts neuroendocrine function via:
    - HPA
        - Hypothalamus controls anterior pituitary via hormone secretion into hypophysial portal system
        - Hypothalamus controls posterior pituitary via direct innervation
        - Ant + post pituitary secrete number of hormones
    - Pineal gland
        - Innervated by ANS
        - Receives signals from suprachiasmatic nucleus of hypothalamus

Hormones	Action	Regulation
GH	stimulates IGF-1 → skeletal growth ↑protein synthesis anti-insulin → ↑[glucose]	↑: starvation, amino acid, hypoglycaemia, exercise ↓: somatostatin
ACTH	↑steroid synthesis → ↑cortisol stress response	↑: stress ↓: glucocorticoids (negative feedback)
LH	luteinisation of ovarian follicle LH surge → ovulation	↑: GnRH ↓: prolactin
FSH	stimulates ovarian follicle development spermatogenesis	↑: GnRH
Prolactin	mammary gland hypertrophy milk production inhibits LH	↑: suckling ↓: dopamine
ADH	V_1 = vasoconstriction V_2 = ↑aquaporin → ↑H_2O reabsorption	+: ↑osmolality, ↓volume, ATII, stress –: ↓osmolality
Oxytocin	mammary gland contraction uterine contraction → labour mood	
Melatonin	Regulates circadian rhythm	+: circadian pacemaker, darkness –: bright light

NEUROLOGICAL PHARMACOLOGY

Outline the pharmacology of anti-depressant, antipsychotic, anti-convulsant, anti-parkinsonian and antimigraine medication

Antidepressant

Classify drugs used in the treatment of depression. Outline the interactions between antidepressant drugs and drugs that are commonly used during the perioperative period: PAST QUESTION

Antidepressants aim to alleviate depression by ↑availability of 2 key monoamine NTs: NAd + 5HT

Divided into 4 groups:

1. **TCA**
   - E.g.: amitriptyline, nortiptyline, dothiepine
   - 1st generation drugs based on tricyclic ring structure, new drugs different ring numbers
   - MoA:
     - inhibit reuptake of monoamines NAd + 5HT → ↑conc NA + 5HT at synapse
     - block mACh, H1, α adrenoceptors
   - SE:
     - Antimuscarinic/ anticholinergic (↑QTc, widened QRS, RBBB → PEA → refractory to rx; dry mouth, urinary retention)
     - antihistaminergic (sedation)
     - blocks α1 adrenergic (postural hypotension)
   - drug interactions
     - serotonin syndrome
     - phenothiazones (chlorpromazine, promethazine): displaces TCA
     - barbiturates: ↑rate of hepatic metabolism of TCAs → ↓activity
     - amitriptyline ↑CVS effects of adrenaline
2. **SSRI**
   - E.g. Fluoxetine, paroxetine, sertraline
   - MoA: selectively inhibit neuronal reuptake of 5HT → ↑synaptic [5-HT]
   - SE: serotonin syndrome: triad of behaviour, motor, autonomic instability
3. **MAOI**
   - Tranylcypromine, phenelzine, moclobemide
   - MoA:
     - Forms complex with MAO, ↑level of amine NTs (NAd + 5HT)
     - MAO-A: deaminates NAd, 5-HT, Ad
     - MAO-B: deaminates phenylethylamine, tyramine, dopamine
     - Older drugs: non-selectively inibit MAO
     - Newer drugs: reversibly + selectively inhibit MAO-A (MAO-A metabolises monoamines NA, 5HT, DA → therefore MAO-A inhibition → ↑synaptic concentration of monoamine)
   - Drug interactions
     - Hypertensive crisis
       - 1. Tyramine rich foods (cheese, pickled herring, chocolate)
       - 2. Pethidine, indirectly acting sympathomimetics (ephedrine, aramine)
     - serotonin syndrome (most common cause) 2o accumulation of neuronal 5-HT + serotonergic drugs
4. **Atypicals**
   - Lithium
   - Mirtazapine: alpha2 adrenergic antagonist → potentiates NA + 5HT neurotransmission

Table 18.2 Effects of various antidepressants.

	Anticholinergic effects	Sedation	Postural hypotension
TCA			
Amitriptyline	++++	++++	++
Imipramine	++	++	+++
Nortriptyline	++	++	+
Desipramine	+	+	+
SSRI			
Fluoxetine	+	nil	+

	Tricyclics – amitriptyline, dothiepin	**SSRI – fluoxetine, paroxetine, sertraline, venlafaxine**	**MAOI**
Chem	Dibenzocycloheptadiene derivative		
Uses	Antidepressant, sedative, analgesic - Depression - Nocturnal enuresis - Adjunct in rx chronic pain syndromes	Depression, anxiety, OCD, ED	Depression, OCD Chronic pain Migraine Now largely superseded due to side effect profile
Pres	Tablet: 10/25/50mg or syrup 2mg/ml CCS for injection: 20mg/ml amitriptyline hydrochloride	Tablets	
Action	1. **inhibit neuronal reuptake of NAd + 5-HT** 2. Antagonize: - muscarinic ACh Rs - α-1 adrenergic - H1, H2 histaminergic R - NMDA Rs	Selectively inhibit neuronal reuptake of 5-HT	Inhibition of MAO → ↑amine NTs MAO-A deaminates 5-HT + catecholamines MAO-B deaminates tyramine + phenylethylamine
CNS	antidepressant; sedation, weakness	Less sedative	
CVS	postural hypotension, tachycardia, dysrhythmias, ↑conduction time through AV node	Less cardiotoxic in OD	
Resp	resp depression at high doses		
Other		Nausea, constipation May impair platelet function	
Toxicity/ SE	**Anticholinergic effects**: blurred vision, dry mouth, constipation, urinary retention CNS: excitation, seizures, depression, myadriasis, hyperthermia CVS: ↑QTc + wide QRS; ventricular arrhythmias; RBBB; ↓BP **NB drug interactions: serotonin syndrome**	Seratonergic syndrome: hyperreflexia, agitation, clonus, hyperthermia N+V, headache, insomnia, ↓libido	
Route/ dose	PO: initially 75-150mg/day → 50-100mg/day for maintenance IV: 10-20mg 6hrly		
Onset	Takes from 3-30days to become fully effective		
A	bioavailability 50%; peak serum time 4hr	High PO bioavailability	
D	95% protein bound VD ~20L/kg	Highly protein bound, high VD	
M	N-methylation + hydroxylation → subsequent conjugation to glucuronide + sulfate hepatic CYP2C19, CYP3A4; metabolites = nortriptyline	Hepatic Fluoxetine: CYP450	
E	urine (20%); small amounts in faeces Clearance 10-15ml/min/kg Elimination ½ life 13-36hours	Elimination unaffected by renal impairment	

Antipsychotics

Classification of antipsychotics

- Typical (1st generation): ↑affinity for D2 Rs (and therefore less blockade of 5-HT) → ↑effect on +ve symptoms + ↑incidence extrapyramidal side effects
- Atypical (2nd generation): few motor effects; ↑effect on –ve symptoms

MoA atypical antipsychotics

- Antipsychotics mediated in part by blockade of dopaminergic transmission esp limbic system
    - All block D2 receptors
    - Differential blockade of other dopamine receptors / antipsychotic activity: 5-HT2, H1, α1, muscarinic ACh antagonism

Side effects of atypical antipsychotics

Extrapyramidal side effects

- Incidence dose related
    - Highest with haloperidol
    - Lower with chlorpromazine
    - Lowest with newer agents
- Anticholinergic drugs
    - Not routine prophylaxis for EPSE
    - May add to anticholinergic effects of antipsychotics and worsen tardive dyskinesia
- Types of extrapyramidal SE
    - Dystonias
        - Torticollis, carpopedal spasm, trismus, perioral spas, oculogyric crisis, laryngeal spasm
        - More common in young and ↑doses
        - May occur 24-48hrs
        - Respond rapidly to anticholinergics such as benzatropine
    - Akathisea
        - Feeling of motor restlessness
        - Usually 2-3 days (up to weeks) after starting rx
        - Improves with dose ↓
    - Parkinsonism
        - Tremor, rigidity, bradykinesia
        - Develops after weeks to months
        - Short term anticholinergic can help
    - Tardive dyskinesia
        - Involuntary movements of face, mouth, or tongue (sometimes head, neck, trunk, limbs)
        - Usually after medium to long term treatment
        - Slow improvement as drug withdrawn

Neuroleptic malignant syndrome

- Fever, marked muscle rigidity, altered consciousness, autonomic instability
- Progresses rapidly over 24-72hours
- ↑CK + ↑WCC
- Treatment:
    - cease antipsychotic, general supportive care (cooling, vol replacement, treat hyperK)
    - Anticholinergics + benzos may be helpful for muscular rigidity
    - PO bromocriptive or IV dantrolene

	Haloperidol	**Olanzapine**	**Risperidone**	**Quetiapine**
Chem	Butyrophenone derivative		Functional groups: benzisoxazole and piperidine	dibenzothiazepine derivatives
Gen	1st generation/ typical antipsychotic	2nd generation; atypical antipsychotic	2nd generation; atypical antipsychotic	2nd generation atypical antipsychotic
Uses	Antiemetic + neuroleptic Schizophrenia / psychosis Acute confusional states + delirium N+V / pall care Motor tics + hiccupping	Atypical antipsychotic + antimanic + mood stabliliser Schizophrenia Bipolar mania Agitation	Schizophrenia / psychosis / mania Dementia with behavioural disturbance delirium	Schizophrenia / mania / bipolar depressive episodes
Pres	Tablets: 0.5-20mg Syrup: 2/10mg/ml CS for injection 5mg/ml haloperidol Depot: 50/100mg/ml	Yellow crystalline solid Tablets 2.5-20mg	Tablets/ liquid	Tablets
Action	Central dopaminergic **D2 blockade** → - ↓reticular activating system - ↓threshold for vomiting at chemoreceptor trigger zone Post synaptic GABA antagonism	**Dopamine + 5-HT type 2 receptor site antagonism**	Selective monoaminergic antagonist **Antagonist** at: - **5-HT2 receptors** - D1 + D2 Rs (lower affinity) - Alpha1 + alpha2 adrenergic Rs - H1 Rs	**Antagonist of:** - **D1 + D2** - H1 - Alpha1 + alpha2 - 5-HT1A, 5-HT2
CNS	Neurolepsis → ↓motor activity, anxiolysis, ↑seizure threshold		may ↓seizure threshold	
CVS	Minimal; α-adrenergic R antagonist → ↓BP if hypovolaemic		↑QT interval → ↑risk arrhythmia Orthostatic hypotension ↑risk VTE	
Resp	Minimal			
Other	Antiemetic via CTZ Can cause hyperprolactinaemia			
Toxicity/ SE	Extrapyramidal: neuroleptic malignant syndrome (catatonia, CVS lability, hyperthermia, myoglibinaemia) haem + LFT disturbances	Orthostatic hypotension, sedation, extrapuramidal symptoms	Hyperglycaemia, weight gain, akathisia symptoms Postural hypotension (2o alpha blocking) Nasal mucosal swelling	Constipation, weight gain, dry mouth Orthostatic hypotension, seizures, ↑BSL, NMS
Route/ dose	Delirium: IV 1-5mg; IM 2-30mg Psychosis: 1-15mg/day divided doses	IM 5-10mg, PO 5-20mg		
Onset		PO: 6hrs; IM: 15-45min		Immediate release: PO 1.5hr; extended 6hr
A	Bioavailability 50-90%		Bioavailability 70%	Bioavailability 100%
D	92% PB VD 18-30L/kg	93% PB VD 1L	90% PB VD 1-2L/kg	85% PB VD 6-14L/kg
M	Extensive via liver Reduced metabolite may be active	Extensive via liver direct glucuronidation + CYP450 oxidation	Liver by CYP2D6 Metabolite: 9-hydroxyrisperidone	Liver by CYP3A4
E	11ml/kg/min Elimination ½ life 10-40hrs	½ life 20-50hrs (immediate release) Urine 55% + faeces 30%	½ life 3hr (extensive metabolisers) 20hr (poor metabolisers) Prolonged in renal impairment; ↑fraction free drug in hepatic disease Urine 70%; faeces 14%	Immediate release ½ life 6hr; extended 7hr Urine 73% faeces 20%
Special points	Not removed by dialysis		Low incidence EPS Use ½ doses May aggravate parkinsons NB can cause deterioration in Lewy body dementia	

	Dexmedetomidine	**Chlorpromazine**	**Clozapine**	**Lithium**
Chem	Imidazole derivative D-stereoisomer of medetomidine (L stereoisomer inactive)	Phenothiazine (with aliphatic side chain)	tricyclic dibenzodiazepine Atypical (3rd gen)	Alkali metal
Uses	Sedation without respiratory depression Anxiolysis / Analgesia	Schizophrenic + psychoses N+V / Intractable hiccups	Treatment resistant schizophrenia	Antipsychotic Mania / bipolar / affectrive disorders / chronic pain
Pres	CCS 10microg/ml	Tablets: 10-100mg / Syrup 5mg/ml Straw solution for injection as chlorpromazine hydrochloride	Yellow tablet	Tablets 200-450mg lithium carbonate
Action	agonist at post-synaptic **α2 receptors** in locus coeruleus to **↑K conductance → ↓NAd release**	Antipsychotic + antiemetic + sedative **Antagonist** of: - **D2** → ↑threshold for vomiting from CTZ - 5-HT - Histaminergic - Muscarinic cholinergic - α-adrenergic Rs	Selective monoaminergic antagonist Antagonist of - **5-HT antagonist** ($5HT_{1C}$, 5HT2, 5HT3) - D1 + D2 (weak) + D4 (behavioural) - NAd - Histamine R	?stabilisation of membranes or by alteration of central NT function
CNS	Sedation, anxiolysis (low doses – anxiogenic at high doses), amnesia, ↓MAC ↓SNS outflow	Neurolepsis + sedation + anxiolysis ↑effect co-administered analgesics + ↓seizure threshold Skeletal muscle relaxation via central effect Miosis 2o alpha-adrenergic ↓time in REM EEG: slowing + ↑theta + delta wave activity + ↓α+β wave		↓seizure threshold in epileptics Otherwise minimal
CVS	↓MAP ↓HR	-ve inotrope ↓SVR (α-blockade) → postural hypotension + reflex ↑HR ↑corBF Mild quinidine like action ↑PR and QT, T wave flattening, ST segment depression		T wave depression
Resp		Resp depressant ↓bronchial secretions		
AS		↑appetite → weight gain ↓salivation, gastric secretion, GI motility		
Other		↑RBF Impairs temperature regulation by peripheral + central		Polyuria + polydipsia 2° antagonism of effects of ADH Prolonged use: ↑Na (2o ↑aldosterone), ↑Ca2+, ↑Mg2+ Mild insulin like effect on CHO metabolism
Toxicity/ SE	↓BP, ↓HR, nausea, dry mouth	Extrapyramidal: NMS Cardiovascular lability, hyperthermia Anticholinergic effects, blood dyscrasias	Myocarditis (potentially fatal) Seizures Hepatitis Agranulocytosis, thromboembolic disease	**Narrow TI** plasma levels 0.5-1.5mmol/L therapeutic levels: TFT disturbance, weight gain, tremor, pretibial oedema ↑levels: N+V+D, abdo pain, ataxia, convulsions, coma, dysrhythmias Nephrogenic diabetes insipidus 5-20% on long term rx
Route	IV only: 0.2-0.7microg/kg/hr	PO 10-50mg 6-8hrly; IM 25-50mg 6-8hrly		0.4-1.2g/day; monitor serum levels
Onset		30-60min	15min	
Duration		4-6hr immediate; 10-12hr extended release	4-12hr	
A		Bioavailability 30%	Bioavailabilty 50-60%; rapid absorption	Bioavailability 100%
D	94% PB; VD 1.33L/kg; distribution ½ life 6mins	95-98% protein bound; VD12-30L/kg	97% PB; VD 2L/kg	No protein biding; VD 0.45-1.13L/kg
M	extensive hepatic metabolism to methyl and glucuronide conjugates (inactive)	Extensively by liver by oxidation, dealkylation, demethylation, and hydroxylation with subsequent conjugation to glucuronide At least 168 metabolites described; many active	Liver via CYP450 Metabolites: norclozapine May obey 0-order kinetics at upper limit dose range	
E	95% urine elimination ½ life 2hrs clearance 40L/hr	Urine + faeces (equal) <1% unchanged Clearance 6-11ml/kg/min Elimination ½ life 30hrs	½ life 12hr Clearance 200ml/min Urine (50%) + faeces (30%)	95% excreted in urine; remainder in sweat Clearance 0.24-0.46ml/min/kg Elimination ½ life 14-30hrs
Special points	Clearance ↓ in hepatic impairment; no change in renal impairment	Not removed by dialysis		Renal, cardiac, thyroid function monitoring

Anticonvulsant

	Phenytoin	**Na valproate**	**Carbamazepine**	**Levetiracetam**
Chem	Hyantoin derivative	Sodium salt of valproic acid (fatty carboxylic acid)	Iminostilbene derivative – structurally related ot the tricuclic antidepressants	Pyrrolidone derivative
Uses	generalised tonic clonic + partial seizures Digoxin induced arrhythmias Trigeminal neuralgia TCA toxicity	Primary generalised epilepsy esp. petit mal, myoclonic seizures, tonic-clonic Chronic pain	Anticonvulsant + analgesic Trigeminal neuralgia Bipolar disorder	Partial seizures Myoclonic epilepsy + generalized epilepsy
Pres	Capsules; syrup CCS for injection 50mg/ml phenytoin sodium	100/200/500mg tablets syrup 40mg/ml ampoules 400mg lyophilized Na valproate for dilution	100/200/400mg tablets 125/500mg suppositories white syrup 20mg/ml carbamazepine	Tablets: 250-1000mg PO solution IV concentrate 100mg/ml (for dilution)
Action	Anticonvulsant + antiarrhythmic **Stablilses inactive state of voltage gated Na+ channels → limits repetitive generation of APs** - slows inward Na+ during depolarisation in excitable tissue - binds + stabilises inactivated Na channels: prevents durther generation of AP central to seizure activit - blocks Ca2+ flux - delays outward K flux	Anticonvulsant **GABA-ergic inhibition**; Na-valproate ↑brain GABA levels by **inhibition of succinic semialdehyde dehydrogenase in GABA shunt** May mimic action of GABA at post-synaptic recpetors and ↓excitatory inhibition	**Stabilizes voltage gated Na channel in inactivated state** **GABA R agonist**	Antiepileptic **↓intracellular Ca2+ release** **MoA unclear**
CNS	Anticonvulsant by stabilizing seizure threshold + preventing spread of seizure activity	Anticonvulsant Minimal sedation Essential tremor	↑seizure threshold	Somnolence + headache
CVS	Class Ib antiarrhythmic Enhances AV nodal conduction		Antiarrhythmic; ↓AV conduction	
Other	↑BSL	↑NH4	Antidiuretic	Nasopharyngitis in 10%
Toxicity/ SE	**Narrow therapeutic index** Rapid admin → ↓BP, CHB, VF, asystole **dose dependent**: N+V, drowsiness, peripheral neuropathy, behavioural, tremor, vertigo, ataxia **idiosyncratic**: rash, gum hyperplasia, acne, blood dyscrasias, hepatotocicity **Drug interactions:** *potent enzyme inducer with many drug interactions* - induces hepatic enzymes - ↓ effectiveness of benzos, OCP, warfarin - toxicity can be precipitated by metronidazole, isoniazid, chloramphenicol	Hepatic dysfunction, acute pancreatitis, GI upset, hair loss, oedema, weight gain Platelet disturbances: ↓aggregation; thrombocytopenia Coagulation disturbances: ↑bleeding time, ↑PT, ↑APTT Teratogen	Diplopia, headache, drowsiness, ataxia N+V; drug induced hepatitis Antidiuretic effect Rashes 3% Mild neutropenia/ agranulocytosis Aplastic anaemia Teratogen **Induces hepatic enzymes**	Tremor, dizziness, cutaneous rashes
Route/ dose	PO: 200-600mg/day IM 100-200mg q4hr IV: seizures 10-20mg/kg then maint 100mg 6-8hr Cardiac dysrhythmias: IV 4mg/kg	PO: 600-2500mg daily in 2 divided doses IV: 400-2500mg in divided doses Effective plasma range: 40-100mg/L	100-1600mg daily; divided doses	PO or IVI max 1500mg BD
Onset	IV: 0.5-1hr; PO: 2-24hr		Peak serum 4.5hr	Peak serum time <1hr
Duration				
A	Bioavailability 90%	Rapid + PO bioavailability 100%	PO: bioavailability 100%	Bioavailability 100%
D	90% PB VD 0.5L/kg	90% protein bound Vd 0.1-0.4L/kg Brain concentrations 7-30% plasma levels	75% protein bound Vd 1L/kg	Very little protein bound
M	Liver; hepatic hydroxylation (P450) – saturatable: 1st order kinetics → zero order kinetics then conjugated to glucuronide	Liver Oxidation + glucuronidation Some active metabolites	Liver Oxidation to epoxide (active – 30% anticonvulsant properties) Chronic use: induces own metabolism	25% hepatic hydrolysis of acetamide group to inactive metabolite

	Can induce own metabolism + that of other drugs			
E	70% urine (5% unchanged) Clearance 6-10ml/kg/day Elimination ½ life 9-20hrs in 1st order kinetics range Dose ↓hepatic impairment; little alteration in renal impairment	1-3% unahcnaged in **urine** clearance 7-11ml/kg/hour elimination ½ life 8-20hrs	**Urine** as unconjugated metabolites Clearance 20ml/kg/hr Elimination ½ life 16-36hr	95% administered dose excreted in urine ½ life 7hours
Special points		CI in acute liver disease Sedative effects additive with other DNS depressants Not removed by dialysis	NaValproate + CCB → ↑[free carbamazepine] ↓efficacy of panc/ vec	Dose ↓ in pts with moderate to severe renal failure Does not interact with CYP450 system

	Phenobarbital	**Thiopentone**	**Lamotrigine**	**Gabapentin**
Chem	Barbiturate	Thiobarbiturate		Acetic acid derivative (structural analogue of GABA)
Uses	Epilepsy – simple + complex (partial) seizures Generalized tonic clonic, neonatal, febrile seizures	induction of anaesthesia mx of status/ cerebral protection	Focal (partial) and generalized seizures Bipolar disorder (prevention of depressive episodes)	Anticonvulsant + analgesic Neuropathic pain Partial seizures
Pres	CCS for injection PO tablets	yellow powder of thiopental sodium + 6% sodium carbonate, stored under atmosphere of N2 reconstituted in water prior to use → 2.5% solution		600/800mg tablets + capsules
Action	Prolong inhibitory postsynaptic potential by ↑mean Cl channel opening time and duration of GABA induced cell membrane hyperpolarization	enter CM in unionized form → ionized → membrane stabilizing effect by ↓Na+ and K+ conductance → ↓amplitude of AP; ↓rate of conduction Inhibit Ca2+ dependent NT release + ↑Cl ion conductance in absence of GABA	Stabilizes presynaptic neuronal membranes **by:** - **blocking voltage-dependent Na+ channels** on neurons that produce glutamate + aspartate → **inhibiting glutamate** release	Structurally related to GABA; doesn't interact with GABA Rs Binding site: **α2-delta subunit of voltage gated Ca2+ channels** May also: - partially ↓response to glutamate agonist NMDA - ↓release of monoamine NTs - stimulate glutamate decarboxylase - ↑synaptic release of GABA
CNS	Sedative hypnotic + anticonvulsant	smooth rapid induction of anaesthesia; ↓CBF, ↓ICP, ↓IOP anticonvulsant		Analgesic Anticonvulsant
CVS		-ve inotrope; ↓CO ~20%; ↓SVR → ↓BP		
Resp		potent resp depressant; ↓response to hypercapnia; occasional laryngospasm/ bronchoconstriction		
AS				
Other		splanchnic constriction; ↓RPF; ↑ADH, ↓UO		
Toxicity/ SE		Extravasation → tissue necrosis	Severe skin reactions: SJS Pancreatitis, hepatotoxicity	**Neuro**: Dizziness, ataxia, nystagmus, somnolence, tremor, diplopia Leucopenia, weight gain, viral infections
Route/ dose	IM 100-300mg anticonvulsant 10-20mg/kg status	IV 2-7mg/kg		PO: initially 300mg TDS up to 1800mg/d
Onset	IV 5min	30s	1hr immediate release; >4hrs extended release	Peak plasma levels <2-3hrs
Duration	4-6hr	5-15min; cumulative with repeated admin		
A	PO: bioavailability 70-90%		Bioavailability 98%	Bioavailability 60%
D	Low lipid solubility 40% PB	70% protein boun; 40% sequestered in RBCs; Vd 2L/kg	55% PB VD: 1L/kg	**Not bound to plasma proteins** Vd 0.85L/kg
M	Hepatic; converted via oxidative hydroxylation to p-hydroxyphenobarbitone (inactive)	liver: side arm oxidation to pentobarbital + ring cleavage to urea + 3carbon fragments	Hepatic + renal through glucuronidation Metabolites inactive	**Not metabolised**
E	25% unchanged in urine	**urine** as inactive metabolites (0.5% unchanged);		**Renal; unchanged**

	75% renal ½ life 50-140hrs	clearance 4ml/kg/min elimination ½ life 3-22hr		Elimination ½ life 5hrs Clearance directly proportional to creatinine clearance
Special points	Potent inducer of CYP450 system Monitoring of plasma concentrations	rapid onset due to lipophilicity + low degree of ionization		Should be weaned if discontinuation of therapy regardless of indication ↓in renal impairment

Antiparkinsoniuan

	Levodopa	**Carbidopa**	**Bromocriptine**	**Nimodipine**
Chem	Precursor of dopamine	Peripheral decarboxylase inhibitor	Synthetic dopamine agonists	Dihydropyridine
Uses	Parkinsons disease	Parkinsons disease		Prevention and rx of cerebral vasospasm 2` to SAH Migraine, CVA, drug resistant epilepsy
Pres				IVI 200microg/ml of niodipine containing ethanol 20% and macrogol 17% and as 30mg tablets
Action	1% crosses BBB → converted to dopamine rest decarboxylated to dopamine in liver (cannot cross BBB) coadministration with peripheral decarboxylase inhibitor → ↑proportion of levodopa crossing BBB, ↓side effects	Pharmacologically inactive when administered alone Combined with levodopa → inhibit dpoa decarbodylase		Dilation of cerebral vessels → ↑cerebral perfusion Ca2+ antagonist that binds to specific sites on cell membranes od vascular smooth muscle + prevents Ca2+ influx through "slow" Ca2+ channels → vasodilation Relatively specific action on cerebral arterioles
CNS	Nausea Abnormal involvuntary movements: dyskinesia, oxylogyric crisis, behavioural distirbances		↓secretion groeth hormone orthosttic hypotension dyskineasia, nausea	↑cerebral blood flow up to 18% in SAH
CVS	Orthostatic hypotension Arrhythmias			↓SBP ↓DBP ↓SVR ↑CO by 25-45%
Resp				
AS				
Other				
Toxicity/ SE				Flushing, headache, nausea, hypotension, reversible LFT abnormalities
Route/ dose				CVC 1mg/hr for 2hours then 2mg/hr for 5-14 days PO: 60mg q4hr within 4 days of SAH
Onset				
Duration				
pKa				
A				Bioavailability 3-28%
D				98% PB; VD1-2L/kg
M				Demethylated + dehydrogenated to inactive pyridine analogue
E				50% urine; 30% faeces Clearance 400L/hr ½ life 1-7hrs ↓clearance in hepatic failure
Special points				

Antimigraine

Outline the pharmacology of histamine antagonists

Histamine

- Non mast cell mediated histamine = NT
- Location: cerebral cortex, spinal cord, gastric mucosa, mast cells, pituitary gland, body surfaces
- Synthesis: decarboxylation of amino acid histidine
- **3 subtypes**
  - **H1:**
    - GPCR → phospholipase C → IP3, DAG → ↑Ca2+
    - CNS: post synaptic excitatory
    - CVS: ↓conduction AV node, Cor vasoconstriction
    - Vessels: vasodilation 2o ↑NO, ↑permeability, ↑prostacyclin production (vasodilation, ↓platelet aggregation, ↑airways resistance)
    - Resp tract: ↑bronchial smooth muscle tone; ↑mucous
    - Skin: stimulation of cutaneous nerve endings → pruritis
  - **H2**
    - GPCR → ↑AC → ↑cAMP
    - CNS: post synaptic inhibitory
    - CVS: Cor vasodilation, +ve inotrope/ chronotrope
    - GIT: ↑gastric acid production (parietal cells)
  - **H3** (only in research)

Pharmaceutics

- 1st generation: competitive antagonist that produce sedation with muscarinic, 5HT, αeffects → antihistamine, antiemetic, sedation e.g. promethazine
- 2nd generation (inverse agonists): minimal sedation e.g. loratidine, fexofenadine (telfast)

Pharmacokinetics

- absorption: well absorbed PO; extensive 1st pass metabolism
- distribution: high protein binding, 2nd generation don't readily cross BBB
- excretion: t ½ β variable = 8hours
- onset of action: <2 hours
- duration of action: 1st gen 4-6hrs, 2nd 12-24hrs

pharmacodynamics

- ↓effects H1 Rs: ↓vasodilation, ↓urticaria/ angioedema, ↓bronchoconstriction, ↓nausea
- 1st gen can produce anticholinergic effects: dry mouth, dry skin, blurred vision, confusion, sedation, flushing
- CVS: dysrhythmias
- CNS: seizures, coma, death

Outline the pharmacology of drugs acting via effects on serotonin or serotonin receptors

5-HT R

- Function :
  - Excitatory on pathways involved in control of muscles
  - Inhibitory on pathways that mediate sensations
  - 5HT = vasoactive substance: vasoconstriction of cerebral / cor / pulmonary
  - NT: emesis + pain
- Location:
  - Brain: hypothalamus, limbic system, SC, retina, cerebellum
  - Platelets
  - smooth muscle + GIT
  - pre + postsynaptic
- **Synthesis**: hydroxylation + decarboxylation of essential aa tryptophan
- Fate:
  - active reuptae
  - inactivated by MAO → 5-hydroxyindoleacetic acid → renally excreted
- **7 subtypes of 5-HT R**
  - Most coupled to G proteins and produce effect via AC or PLC (exception is 5HT3 = ion channel)
  - Effect varies with each R
  - **$5HT_1$:** Gi → ↓AC → ↓cAMP
    - 1a, 1b: CNS: behavioural effects (sleep, thermoreg)
    - 1d: CNS: vasoconstriction
  - **$5HT_2$:** GP → ↑phospholipase C → ↑IP3, DAG → ↑Ca2+
    - 2a: CNS/PNS, smooth muscle contraction, platelet aggregation
    - 2b: gastric fundus → ↑contraction
    - 2c: CNS: ↑CSF production
  - **5HT3:** direct activation Na+ K channels
    - CNS/PNS: visceral pain, N+V (CTZ), anxiety
  - **5HT4-7:** Gs → ↑AC → ↑cAMP; in brain

Drugs acting via effects on serotonin or serotonin receptors:

1. ***Drugs acting on serotonergic neurotransmission***
   - Use: depression, anxiety
   - Classification:
     - **Degradation inhibitors: MAOI**
       - MOAI
         - MAO = key enzyme for serotonin, dopamine, NAd inactivation
         - MAOI prevent inactivation of monoamines within a neuron → ↑NT to diffuse into synaptic space
         - E.g. phenelzine, selegiline
     - **Storage inhibitors**: amphetamine, methylphenidate, modafinil
       - Interfere with ability of synaptic vesicles to store monoamines
       - Displace 5-HT, dopamine, NAd from storage in presynaptic nerve terminals
     - **Reuptake inhibtors:** SNRI, SSRI, TCA
       - SNRI: block 5HT and NAd reuptake in conc-dependent manner

- SSRI: block reuptake of 5HT → ↑conc in synaptic cleft → ↑postsynaptic neuronal activity
- TCA: inhibit reuptake of 5HT + NAd from synaptic cleft by blocking reuptake transporters → enhancement post-synaptic response

2. ***Serotonin agonists***
   - Role: depression, anxiety, abortive measures in migraine
   - Classification:
     - **Selective**
       - 5HT1A agonist e.g. buspirone
       - 5-HT1B and 5HT1D agonists: triptans
       - 5HT2 agonist: trazodone
       - 5HT4 agonist: cisapride
     - **Non selective**
       - Ergotamine, LSD
3. ***Serotonin antagonists***
   - Role: HTN, antipsychotics, nausea + vomiting
   - Classification:
     - 5HTA/2C antagonists: e.g. atypical antipsychotics (clozapine)
     - 5-HT3 antagonists e.g. ondansetron

Discuss the clinical features and management of serotonin syndrome

Serotonin syndrome

- Classically triad of:
  - Change in mental status: agitation, delirium, restlessness, disorientation, lethargy, seizures, hallucinations
  - Autonomic dysfunction: diaphoresis, HTN, hyperthermia, vomiting, ↑HR, dilated pupils, unreactive pupils, diarrhoea, abdo pain
  - Neuromuscular excitability: myoclonus, tremor, muscle rigidity, hyperreflexia, nystagmus
  - Other: rhabdomyolysis, acute renal failure, DIC, circulatory failure
- Primarily involves overstimulation of 5HT1a and 5HT2 Rs in central grey nuclei + medulla

Diagnosis = clinical

- Pt had serotonergic agent +
- Spontaneous clonus
- Inducible clonus + agitation or diaphoresis
- Ocular clonus + agitation or diaphoresis
- Tremor + hyperreflexia
- Hypertonis
- Temp >38 + ocular clonus or inducible clonus
- DDx: NMS, anticholinergic toxicity, MH, sympathomimetic toxicity, encephalitis

Table 1: Serotonin syndrome and neuroleptic malignant syndrome: distinguishing features. (Source: Up-to-date internet based resource).

	Serotonin syndrome	Neuroleptic malignant syndrome
Onset	Within 24 hours	Days to weeks
Neuromuscular findings	Hyperreactivity	Muscular rigidity, bradyreflexia
Causative agents	Serotonin agonist	Dopamine antagonist
Treatment agents	Benzodiazepines, Cyproheptadine	Bromocriptine
Resolutions	Within 24 hours	Days to weeks

Treatment

- NB if both MAOI + SSRI coingested (even low doses) rapid deterioration + death is well documented if appropriate intervention not promptly initiated
- Prinicples of treatment
  - Ceasing all drugs acting on serotonin
  - Supportive care: O2, IVF, cardiac monitoring
  - Agitation: BZD (also have +ve effect on ↑BP and ↑HR)
  - Autonomic instability: short acting agents e.g. esmolol
  - Hyperthermia: I+V+paralysis
  - Serotonin antagonists if available: e.g. cryptoheptadine
    - H1Rantagonist with non-specific 5HT1 and 5HT2 antagonistic properties
    - Evidence lacking

Table 2: Drugs that can precipitate serotonin syndrome

Mechanism of action	Example
Increased serotonin formation	L-tryptophan
Increased serotonin release	Cocaine
	Ecstasy
	Amphetamines
	Alcohol
	Dopamine agonists
Reduced serotonin reuptake	SSRIs
	Serotonin Noradrenaline reuptake inhibitors
	SNRIs
	TCAs
	Pethidine
	Tramadol
	Fentanyl
	Ondansetron/Granisetron
	St. John's wort
Inhibits serotonin metabolism	MAOIs
Serotonin agonists	Triptans
	Ergot alkaloids
	LSD
Increases sensitivity of the postsynaptic receptor	Lithium