RMS Exam Revision

Year 1, Part 3

Locomotor, Neurology and Pharmacology

Information in this tutorial has been adapted from the RMS Revision Notes – Fundamentals of Medicine & Locomotor

Calcium Homeostasis

Calcium Homeostasis

Normal: 2.2-2.6mmol/L

- Hypocalcaemia: increased neuromuscular excitability and include muscle spasms, tetany and cardiac dysfunction

  <2.2mmol/L

- Hypercalcaemia: NS depression, fatigue, nausea, depression, “stones, bones, groans”

  >2.6mmol/L

Body Distribution of Calcium and Phosphate

- Intracellular: sequestered in mitochondria and endoplasmic reticulum
  - Intracellular free calcium concentrations fluctuate greatly for intracellular signally, enzyme activation and muscle contractions
- Calcium in blood and extracellular fluid
  - 50% of calcium in blood is bound to proteins
- Bone calcium: vast majority of bone calcium
  - 99% in mineral phase
  - 1% in a pool that can rapidly exchange with extracellular calcium

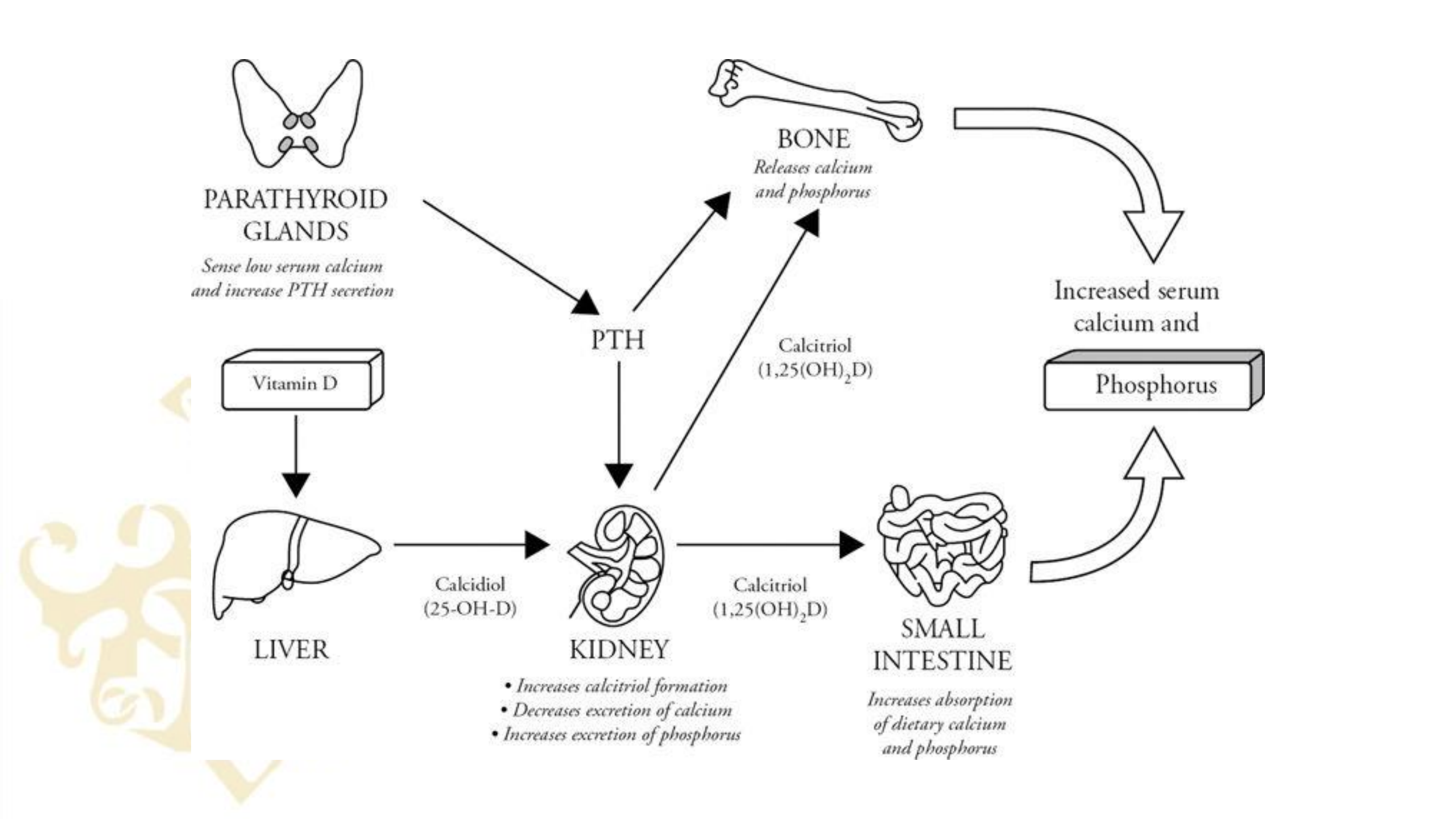
- ~85% of body phosphate is in the mineral phase of bone

Organs involved in Calcium Homeostasis

- Small intestine: site where dietary calcium is absorbed
  - Efficient absorption of calcium in the small intestine is dependent on expression of a calcium-binding protein in epithelial cells
- Bone: calcium reservoir
- Kidney: calcium resorption and excretion

Hormonal Control Systems

- Parathyroid hormone: increases blood calcium
  - Stimulates production of the biologically-active form of vitamin D within the kidney
  - Facilitates mobilisation of calcium and phosphate from bone
  - Maximises tubular reabsorption of calcium within the kidney
- Vitamin D: increases blood calcium
  - Most important effect: facilitates calcium absorption in the small intestine
- Calcitonin: decreases blood calcium
  - Suppression of renal tubular reabsorption of calcium
  - Inhibition of bone resorption


PARATHYROID GLANDS
Sense low serum calcium and increase PTH secretion
BONE
Releases calcium and phosphorus
PTH
Calcitriol (1,25(OH)2D)
Increased serum calcium and Phosphorus
Vitamin D
LIVER
Calcidiol (25-OH-D)
KIDNEY
• Increases calcitriol formation
• Decreases excretion of calcium
• Increases excretion of phosphorus
Calcitriol (1,25(OH)2D)
SMALL INTESTINE
Increases absorption of dietary calcium and phosphorus

The Cell Biology of Connective Tissues

Hyaline Cartilage (e.g. articular cartilage)

- Type II collagen mainly – arranged in a ‘basketweave’ network
- **Chondrocytes** elliptical at surface, sphero-columnar clusters further in
- Absorb shock, load bearing, distributes load and protects ends of bones
- Provide low-friction surface for articulating joints with **synovial fluid**
- Found it: sternal parts of the ribs, the nose, trachea, bronchi, larynx
  - Provides scaffold during development, forms most of the embryonic skeleton

Fibrocartilage

- Type I & II collagen in thick parallel bundles. Less matrix content than hyaline
- Cells usually in rows separated by coarse type I collage – mainly fibroblasts
- Provides support, spreads load, prevents bone-bone contact and limits movement
- Found in high-pressure areas – e.g. IV discs, knee joint, pubic symphysis

Elastic Cartilage

- Essentially identical to hyaline, with an abundant network of fine elastin fibres
- Chondrocytes in lacunae (higher density than hyaline)
- Great flexibility (highly deformable) while maintaining structure (reversible)
- Found in: the auricle of the ear, epiglottis, Eustachian tubes

Cartilage type	Description	Function	Location	Cells and ECM
Hyaline	▪ Amorphous, glassy, blue-white, shiny, ▪ Firm matrix ▪ Many collagen fibrils forming imperceptible network.	▪ Firm support with some pliability. ▪ Spreads load. ▪ Resists forces of compression well. ▪ Can resist (some) tensile force at superficial zones	Most abundant type; Articulating surfaces of moveable joints: ▪ Anterior rib ends ▪ Parts of larynx ▪ Trachea, bronchi Embryonic skeleton	▪ Cell density low (1-10%); ▪ Chondrocytes in lacuna (chondron) and usually solitary; ▪ Collagen mainly type II in basketweave pattern; ▪ Proteoglycans mainly aggrecan.
Fibro-cartilage	▪ ECM similar to hyaline ECM. ▪ Thick parallel collagen fibres	▪ Tensile strength ▪ Withstands (some) compression ▪ Fibro-cartilaginous under tension ▪ Hyaline under compression.	Where hyaline meets true ligament or tendon. Structural intermediate between hyaline and dense connective tissues (e.g. tendon, ligament): ▪ Intervertebral discs ▪ Knee joint menisci	Low cell density. Cell type depends on location: ▪ Tension: fibroblasts ▪ Compression: chondrocytes Collagen mainly type I (tension), some type II (compression). Some aggrecan and small PGs.
Elastic	▪ Like hyaline. ▪ More elastin as a thread-like network. ▪ Some collagen orientation.	Maintains shape of structure while allowing great flexibility.	▪ External ear (pinna) ▪ Epiglottis.	▪ Cells relatively high density. ▪ Chondrocytes in lacunae. ▪ Synthesise some collagen and PGs ▪ Mostly elastin.

Matrix Turnover and Repair

- Usually balanced, normal dynamic loading: “synthesis = breakdown”
  - Greater loading (in range): “synthesis > breakdown”
  - Lesser loading (in range): “synthesis < breakdown”
- Cartilage degeneration: “breakdown >>> synthesis”
- Impact/excessive loading can cause permanent cartilage damage
- **Loading of cartilage within physiological limits is essential for cartilage health**
- Loss of collagen from cartilage is essentially irreversible
- Current treatment: prevent loss of ECM and hence joint function, counteract the initial pro-inflammatory stimuli
- **Cartilage does not repair effectively, so small changes lead to long-term consequences**

Trauma

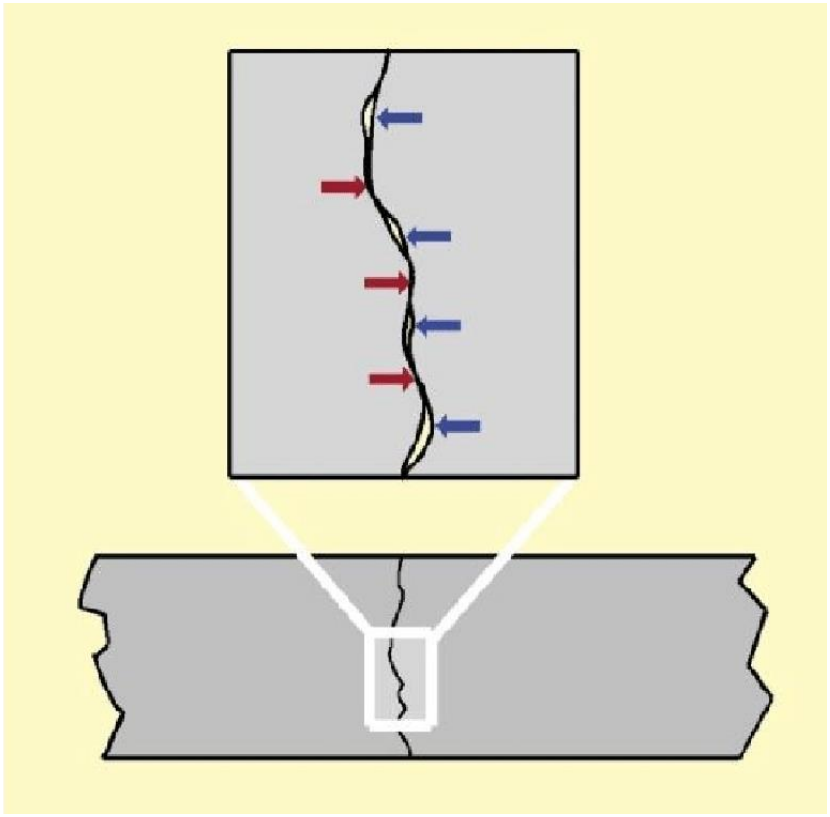
Transferral of energy to the body resulting in tissue damage

Trauma

- Causes of fracture
  - Application of stress which exceed the physiological limits of bone
- Males tend to get more high-energy fractures than females (accidents, sports injuries, etc.)
- Female fracture rate overtakes males at around 40-50 years old from menopause (fragility fractures)
- Fractures can be classified into:
  - High energy (usually poly-trauma, femur/pelvis)
  - Low energy (isolated fractures, forearm)

Direct Bone Healing (Primary)

- Direct healing without fracture callus formation
- Requires edges to be touching exactly with no movement: absolute stability
- Does not occur naturally (i.e. without surgery)
- Important for certain fractures (e.g. intra-articular)



Indirect Bone Healing (Secondary)

- Virtually all other types of bone healing
- Occurs when there is relative stability of the fracture
- Callus forms in predictable pattern:
  - **Inflammation (haematoma)**: allows white cells to clean up debris, growth of new blood cells
    - Haematoma and inflammatory cells
    - Osteoblasts and fibroblasts proliferate
    - Granulation tissue forms around bone edges
  - **Repair (soft callus)**: soft callus is made of fibrous tissue (cartilage)
    - Primary soft callus within 2 weeks
  - **Repair (hard callus)**: soft callus progresses to hard callus by conversion to woven bone which connects the bone fragments more solidly and creates more stability at the fracture site
    - Occurs within weeks of fracture
  - **Remodelling**: disordered new bone is replaced with stronger bone with a lamella structure and better blood supply
    - Occurs over months or years
    - Remodelling responds to the mechanical forces transmitted through the bone

Timeframe of Healing

- Healing timeframe
  - Child: 2-4 weeks (varies significantly depending on age and type of injury)
  - Adult
    - Upper Limb
      - Humerus 6-12 weeks
      - Distal radius 5-6 weeks
    - Lower Limb
      - Ankle 6 weeks
      - Tibia 12 weeks (Variable)
      - Femur 24 weeks

Factors that Affect Fracture Healing

- Patient-related factors
  - Smoking
  - Alcohol use
  - Malnutrition
  - NSAID use
  - Co-morbidity: diabetes, vascular insufficiency
- Injury-related factors
  - The energy transfer of the injury
  - Higher energy injuries take more time to heal due to higher extent of injury to bone, soft tissue and neurovascular supply
  - Morphology of fracture
  - Blood supply (scaphoid, talus, femoral and humeral head: AVN)
  - Disrupted blood supply can result in poor healing or avascular necrosis
  - Associated soft tissue injury
  - Soft-tissue interposition between fracture fragments
  - Intra-articular (synovial fluid delays healing)
- Fixation-related factors
  - Adequate fixation (too little or too much stability)
  - Mode of fixation
  - Soft tissue dissection: disruption of blood supply and soft tissue coverage
  - Infection

Principles of Fracture Care

Principles of Fracture Care: Key Questions

- Is an intervention (e.g. manipulation, surgery) required to:
  - Improve position
  - Provide stability
  - Prevent complications/poor outcome (locally / generally)

- What is the risk of not operating?
  - Provides pain relief
  - Facilitates early rehabilitation (e.g. joint ROM; avoid prolonged bed rest in the elderly)

A-E Assessment

- **“ABCDE”** – do not progress until it is completed
- **Airway** management with C-spine control
  - Assess airway patency: chin lift, jaw thrust
  - Assume C-spine injury
- **Breathing** – give oxygen, assess ventilation (resp exam)
- **Circulation -** Assess blood volume and cardiac output
- **Disability** – assess neurological status (AVPU, GCS), level of consciousness, blood glucose
- **Exposure** – remove clothing for examination, maintain heat

Limb-Threatening Trauma

Open Fractures

- Direct communication between fractured bone and external environment (previously known as a compound fracture)
- Types:
  - In-out open fracture: bone penetrates skin
    - Bone may remain outwith the skin or reduce spontaneously
  - Skin penetrated from outside: open fracture by virtue of soft tissue damage
- May be dramatic and immediately apparent, or may be more subtle
- Prompt management is imperative
  - Extremely high risk of infection (limb and life-threatening)
  - High risk of enduring soft tissue injury
- **Immediate IV antibiotics** and urgent surgery

Arterial Injury

- Damage to a major blood vessel which threatens, or has the potential to threaten, perfusion to the distally-supplied structures
- Always significant and requires urgent referral
- Knee dislocation has a very high incidence of associated NV injury (up to 50%)
- Features (**6Ps**)
  - Signs (pallor, pulseless, perishingly cold)
  - Symptoms (pain, paraesthesia, paralysis)
  - Pooling blood (expanding haemotomas)
- Management:
  - ATLS approach with analgesia and fluid resuscitation
  - Correct likely cause (e.g. reduce joint dislocation)

Nerve Injury

- Damage to neural tissue that results in impaired innervation of distal structures
- Features: characterised by loss of motor or sensory function of the impaired nerve
  - Signs (local trauma, paralysis e.g. wrist/foot drop, arreflexia)
  - Symptoms (pain, paraesthesia, paralysis)
- Dermatome Markers:

- Upper Limb
  - C5 – Deltoid
  - C6 – Thumb
  - C7 – Middle finger
  - C8 – Little finger
- Trunk
  - T4 – Nipple
  - T8 – Xiphisternum
  - T10 – Umbilicus
  - T12 – Pubic symphysis
  - L1 – Groin crease
- Lower Limb
  - L4 – Medial malleolus
  - L5 – Dorsum of foot
  - S1 – Lateral border of foot
  - S3 – Ischial tuberosity
  - S4/5 – Perianal region

Compartment Syndrome

- Swelling into fascial compartment – usually in forearm or lower leg
- **Compression of nerves, blood vessels and muscle inside a closed space**
- Damage to muscle and neurovascular bundle – necrosis occurs
- Pain is the most common sign – **both active and passive stretch**
- Pulse and sensation are late determinants (don't rely on them)
- Most common with tibia fractures due to small compartments
- Complications can be treated by monitoring compartment pressure
- Treatment: **emergency fasciotomy**

Sports Injuries

Sports Injuries

- Sprain: a stretching or tearing of ligaments
- Strain: an overstretching or tearing of a muscle
- Tendonitis: inflammation of a tendon, most commonly from overuse but also from infection or rheumatic disease
  - Lateral epicondylitis: an overuse injury that is due to inflammation or microtearing of the extensor tendons of the arm
- Preventing injury:
  - Warm up and cool down
  - Use proper technique and know when to stop

Rheumatoid Arthritis

Autoimmune

Rheumatoid Arthritis

What is RA?

- **Chronic inflammation** mainly affecting the joints which results in **synovitis.**
- Synovitis can lead to **destruction of articular cartilage** and **ankylosis1/ossification** of affected joint.
- **Systematic effects** – other joints such as skin and blood vessels can be affected in the condition.

Epidemiology

- ~1% of the world's population affected by RA,
- Affects females more (female to male ratio = 3:1)
- Peak incidence in young adults and premenopausal women (decades 3 to 5).
- Most common inflammatory joint disease.
- Costs £1.3b per year. Severe, uncontrolled RA increases mortality, ↓LE by 4 years.

Rheumatoid Arthritis

Pathology

- In the affected joints, the synovium is swollen (oedematous) and its vascularity is increased
- Stroma of the synovium is filled with lymphoid follicles, plasma cells and macrophages
- Instead of the synovial surface being increased, it is turbid and the fluid contains neutrophils
- Inflamed synovium invades articular cartilage (forming a pannus); underlying cartilage eroded
- Cytokines and other mediators released by the synovial and inflammatory cells cause erosion of the cartilage and also activation of osteoclasts leading to the erosion of bone
- When the articular cartilage on the two bone ends has been completely eroded, the pannus fills the space between the two bones: a fibrous and then a bony ankylosis occur
- The inflammation can also cause damage to ligaments and muscles around the joint

Rheumatoid Arthritis

Typical presentation

- **Joint stiffness** (morning and after rest)
- **Joint pain** (difficulties with daily activities)
- Flare-ups and remissions
- Joint structure damaged – weak ligaments, tendons/muscles around hands, reduced grip/dexterity
- Disuse atrophy, muscle wasting

Clinical features

- Ulnar deviation of hands
- Swelling of MCPJ and ICPJ
- Swan neck deformities
- Z thumbs ('Boutonniere')
- Finger drops
- Serositis
- Rheumatoid nodules
- Vasculitis
- Dropped arches
- Turning of knees
- Subluxation (partial dislocation)

Osteoarthritis

Mechanical: wear & tear

Osteoarthritis

- Degenerative joint disorder resulting from **progressive destruction of the joint articular cartilage**
- Primary form is not inflammatory
- Better described as a disorder or syndrome rather than a disease, since it is probably multifactorial

Epidemiology

- Most common degenerative joint disorder (affects elderly, females, and Caucasians more)
- Causes cartilage failure, reduction of mechanical resilience of cartilage, depletion and loss of the ECM until bone rubs and bone and the joint is unusable
- Peak incidence in the 50s (probably as part of the ageing process); usually only one joint is affected
- ~85% of people have evidence of OA by 65 years of age, but only ~25% are symptomatic

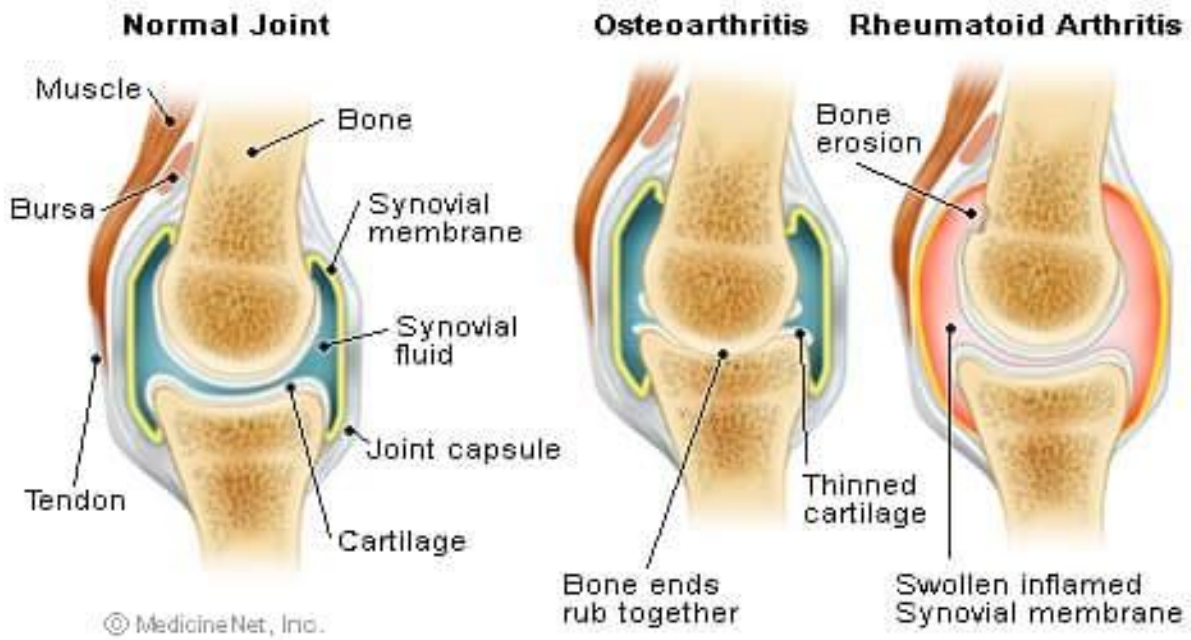
Osteoarthritis

Causes

- Mechanisms underlying the initiation and progressive changes

Possibilities:

- **Normal load on abnormal cartilage** – resulting from inflammation, metabolic/genetic diseases, ageing, toxins and toxic metabolites
- **Abnormal load on normal cartilage** – with obesity, anatomical abnormalities, sub-chondral and gross remodelling of bone, loss of stability, trauma causing abnormal load



Osteoarthritis

Pathology

- Characterised by significant changes in composition and mechanical properties of cartilage
- **Molecular messengers** increased in OA cartilage, responsible for some compositional changes
  - Pro-inflammatory cytokines (IL-1, TNF, NO), degradative enzymes (proteinases, metalloproteinases)
- **Progressive destruction** of the articular cartilage of the joint
- **Joint mice** – full thickness portions of the articular cartilage break off, and enter the joint as loose bodies (‘joint mice’) which can cause further joint damage
- **Bone eburnation** – the exposed sub-chondral bone plate rubs which can be exceedingly painful
- **Sub-chondral sclerosis** – thickening of sub-chondral bone plate and underlying cancellous bone
- **Osteophytes** – bony outgrowths occur at articular surface edges (can be seen on plain x-ray images)
- **Synovial membrane** – much less affected compared to the articular cartilage, but later shows vascular congestion and areas of inflammatory changes and fibrosis

Osteoarthritis

Clinical Features

- **Pain** – subchondral pressure, trabecular microfractures, capsular distension, low-grade synovitis.
- **Functional restriction** – capsular thickening, blocking by osteophytes.
- Loss of movement, pain on movement, restricted range of movement
- Swelling of bone and soft tissue
- Joint crepitus

Osteoarthritis and Rheumatoid Arthritis

	Osteoarthritis	Rheumatoid Arthritis
Aetiology	Mechanical: • localised loss of cartilage • remodelling of adjacent bone • associated inflammation	Autoimmune
Gender	Similar incidence in men and women	More common in women
Age	Seen most commonly in the elderly	Seenn in adults of all ages
Typical affected joints	Large weight-bearing joints (hip, knee) Carpometacarpal joint DIP, PIP joints	MCP, PIP joints
Typical history	Pain following use, improves with rest Unilateral symptoms No systemic upset	Morning stiffness, improves with use Bilateral symptoms Systemic upset
X-ray findings	Loss of joint space Subchondral sclerosis Subchondral cysts Osteophytes forming at joint margins	Loss of joint space Juxta-articular osteoporosis Periarticular erosions Subluxation

Metabolic Bone Disease

Disorders of Bone Remodelling (3)

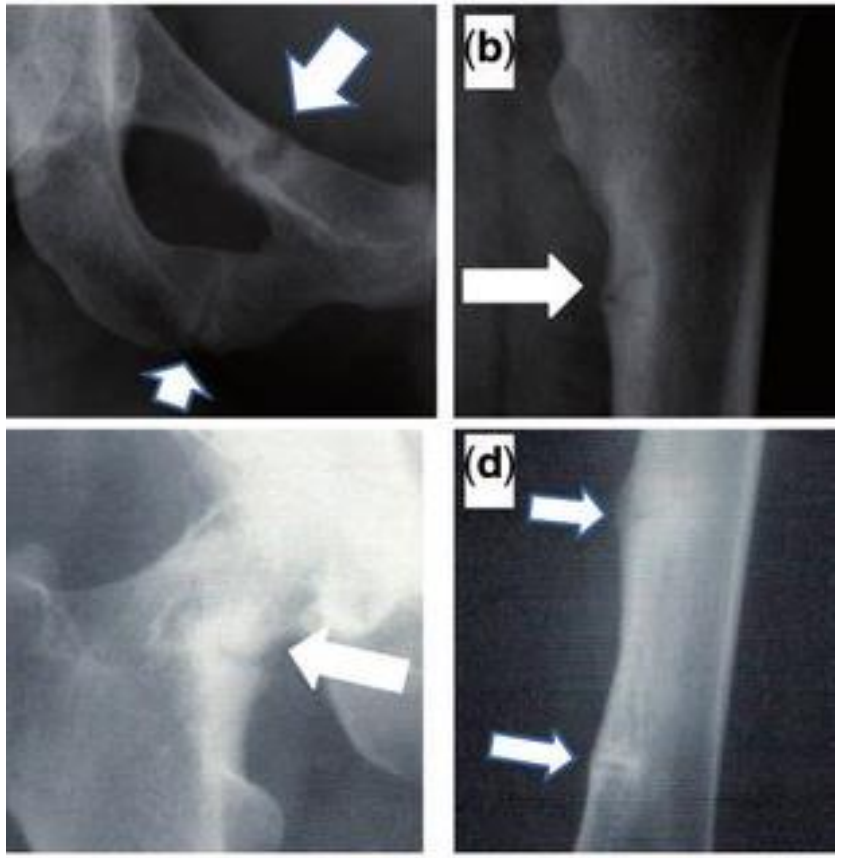
Disorders of Mineralisation (2)

Disorders of Bone Remodelling

- Osteoporosis: resorption > formation
  - Increase of bone loss over bone production. Results from:
    - Age-related changes in bone cell function and activity
    - Reduced physical activity, hormonal influence
    - E.g. osteoporotic vertebrae collapse in the elderly
- Paget's Disease: ↑ resorption, ↑ formation
  - Osteitis deformans – aetiology unknown, often incidental finding
  - Microarchitecture of the Haversian system is distorted ('fluffy' on XR)
  - Signs: pathological #, neuro effects, cranial nerve/spinal cord lesions, OA, sarcomas, cardiac failure
- Osteopetrosis: ↓ resorption (genetic)

Disorders of Mineralisation

- Vitamin D deficiency – osteomalacia, rickets
  - Defective mineralisation of bone due to vitamin D deficiency
  - Microfracture = “Looser’s Zone”
  - Osteomalacia (adults): defective bone mineralisation, bone pain, increased bone fragility, fractures
  - Rickets (children): enlargement of growth plate, bone deformity
- Hyperparathyroidism – affects bone, kidneys, brain, GI



Which of the following statements about osteoarthritis (OA) is true?

A. It is the second most common degenerative joint disorder
B. Men typically suffer OA in the knees and joints of hands
C. PG concentration decreases
D. The interstitial fluid of the ECM in the joint becomes dehydrated
E. Characteristic outgrowths called osteocytes can be detected on X-ray

Answer: C

A- The most common degenerative disorder

B- Women more commonly suffer OA in knees and joints of hands, while the hip joint is more common in men

D- Becomes more hydrated. Dehydration is typical of old age

E- It is osteophytes that are picked up on X-ray

Which of the following is most likely to be released when blood calcium levels are elevated?

A. Vitamin D
B. Calcitonin
C. Parathyroid hormone
D. Thyroxine
E. Oestrogen

B: calcitonin opposes the action of PTH, reducing blood calcium

Which one of the following is a normal level of plasma calcium?

A. 2.1mmol/L
B. 2.7mmol/L
C. 2.4mmol/L
D. 24mmol/L
E. 27mmol/L

C: 2.2-2.6mmol/L is the normal range

Drugs of the Autonomic Nervous System

- Don’t learn the drug – learn the target, and what happens at the receptor

- α agonists: e.g. NA, A and phenylephrine. Indicated for cardio shock and nasal congestion (by vasoconstriction)
- α antagonists: “-zosin”. Indicated for hypertension (by vasodilation), prostatic hypertrophy (contracts prostate).
- β agonists: adrenaline (non-selective) indicated for anaphylaxis and cardiac arrest. Dobutamine for β1 (heart), indicated for heart failure. Salbutamol for β2 (bronchi), indicated for asthma and via IV for premature labour.
- β antagonists: “-olol”. Indicated for hypertension, heart failure, angina (β1) and tremor (β2). Beta-blockers should not be given to asthmatics, as bronchospasm is a side effect and will exacerbate their condition.

Neurology

- **CNS/PNS & motor control**
- **Amyotrophic lateral sclerosis (ALS)**
- **Multiple sclerosis (MS)**
- **Importance of maintaining electrical signalling in the CNS and PNS (neuromuscular control)**
- **Electrically excitable cells – why do we need them?**
- **Action potentials and encoding of information**
- **Neurotransmission & synaptic integration**
- **Excitation contraction coupling and reflexes**

Neurology – CNS and PNS

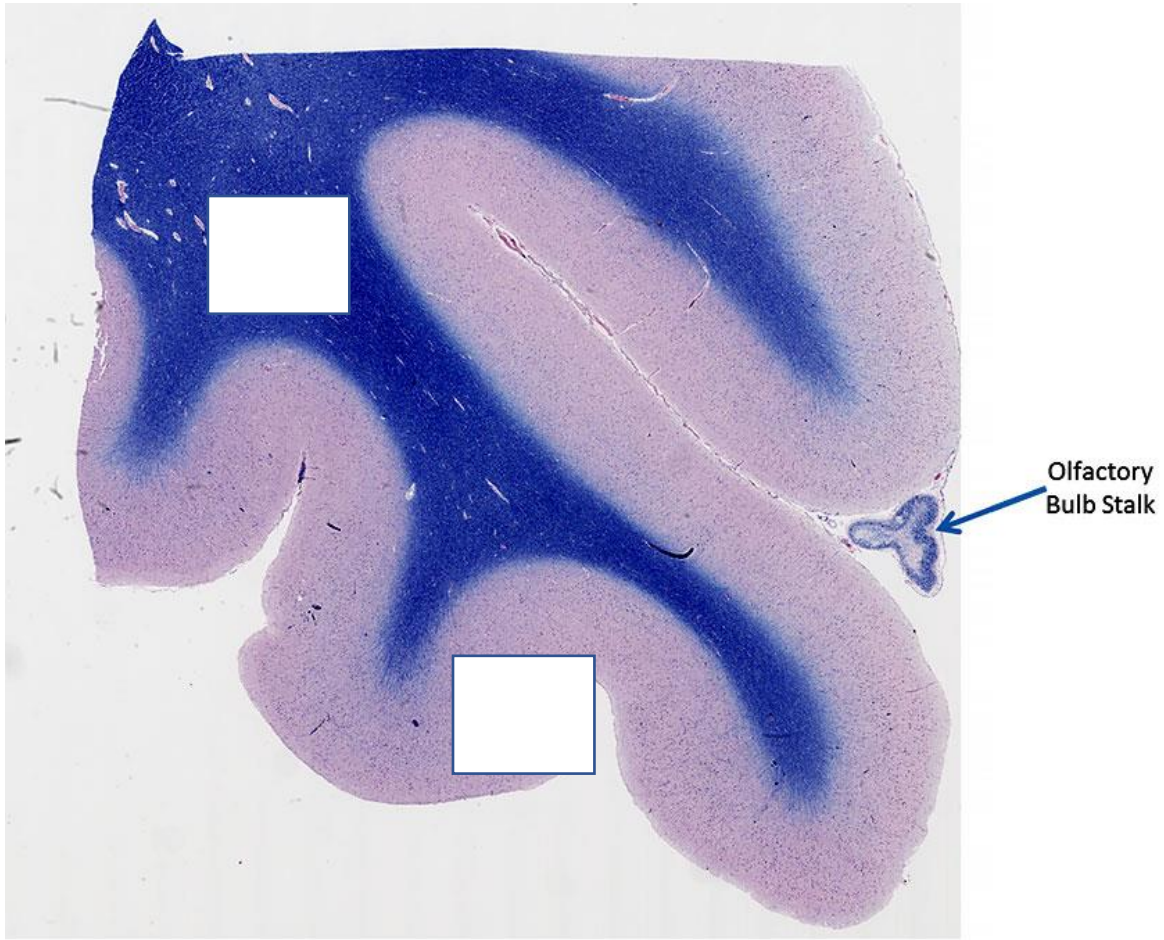
- CNS
- PNS

Neurology – CNS & PNS

- CNS = brain, spinal cord
- PNS = cranial nerves in the head and neck, spinal nerves and ganglia

Neurology – CNS & PNS

- Myelin has been stained blue-black: Which is white matter, which is grey?



Route of Innervation

- Sensory neurones (afferent, dorsal)
- ↓ (input)
- CNS
- ↓ (output)
- Motor neurones: muscles or glands (efferent, ventral)

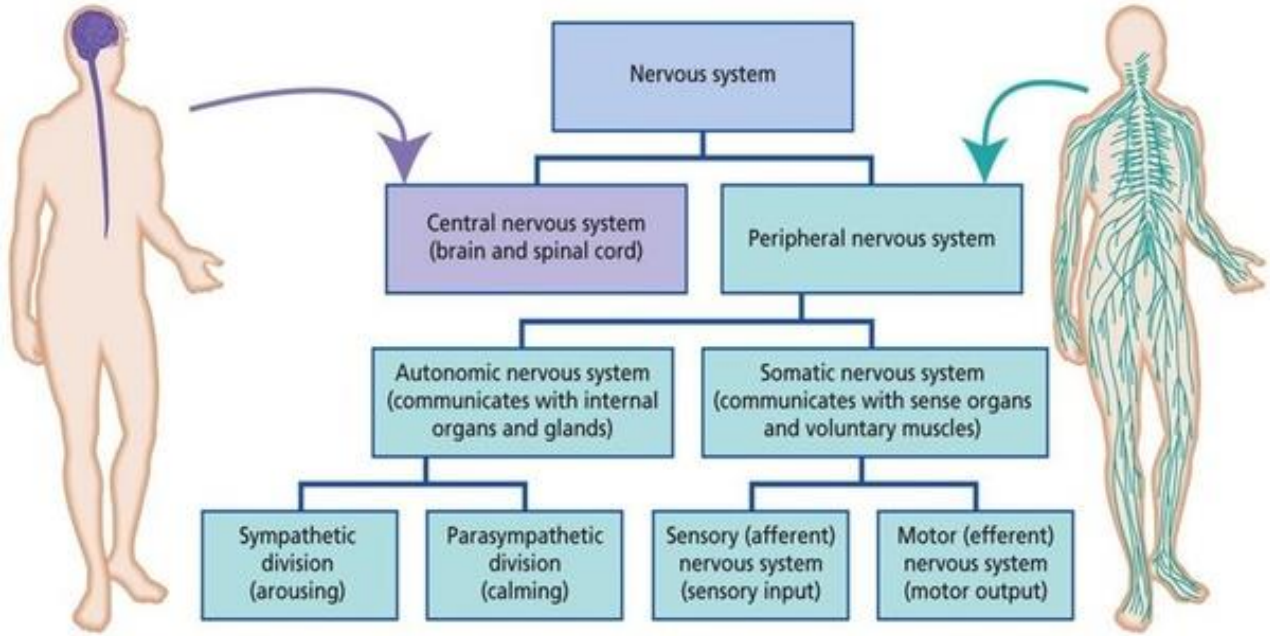
Muscle Innervation/Control

Neurology – Muscle Contraction - Innervation

- SNS – skeletal muscle

under conscious control

ANS – involuntary reactions (smooth muscle, cardiac muscle, gland cells)



Neurology – Sympathetic vs Parasympathetic

- Sympathetic nervous system
- Parasympathetic nervous system

Neurology – Sympathetic vs Parasympathetic

- Sympathetic nervous system:

stress (such as being chased) causes stimulation of sympathetic neurones that , initiates a huge variety of responses necessary to deal with the situation: the heart rate increases to pump more , blood to skeletal muscles, the airways dilate to get more oxygen and digestion is inhibited so that energy is not used unnecessarily. This is known collectively as the “fight or flight” response, evolutionarily preparing the body to fight or run away from a predator. Pre-ganglionic neurones release ACh and post-ganglionic release noradrenaline (NA), so the receptors within the ANS are known as adrenoceptors. Adrenaline (Adr) stimulates the body using this pathway and as such is used to treat cardiac arrest.

- Parasympathetic nervous system: has the opposite effect on the body to the sympathetic NS and dominates during rest, so reduces the heart rate and promotes digestion and excretion. All neurones within this system release ACh and neurones travel long distances to target organs, since most originate in the cranial (neck) spinal cord.

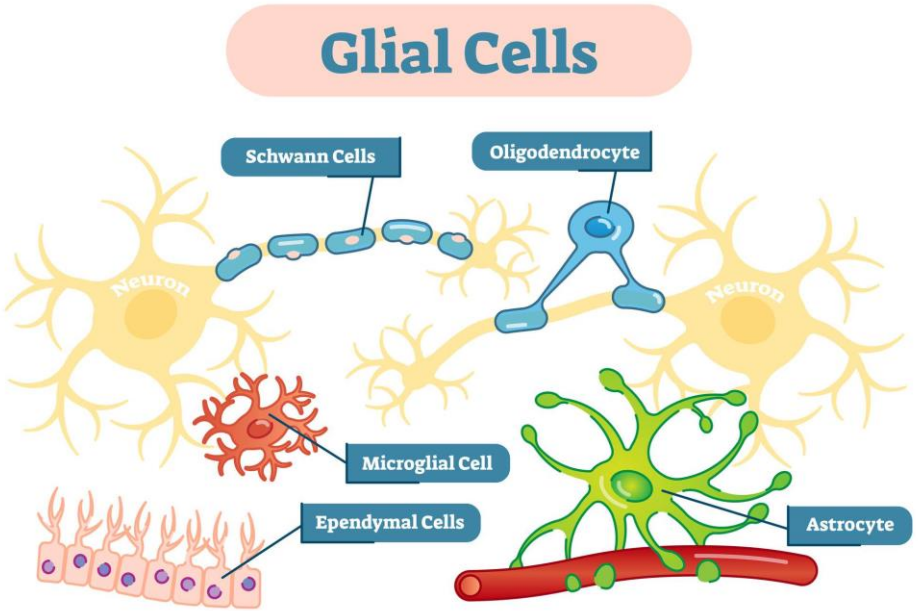
Neurology – Sensory input

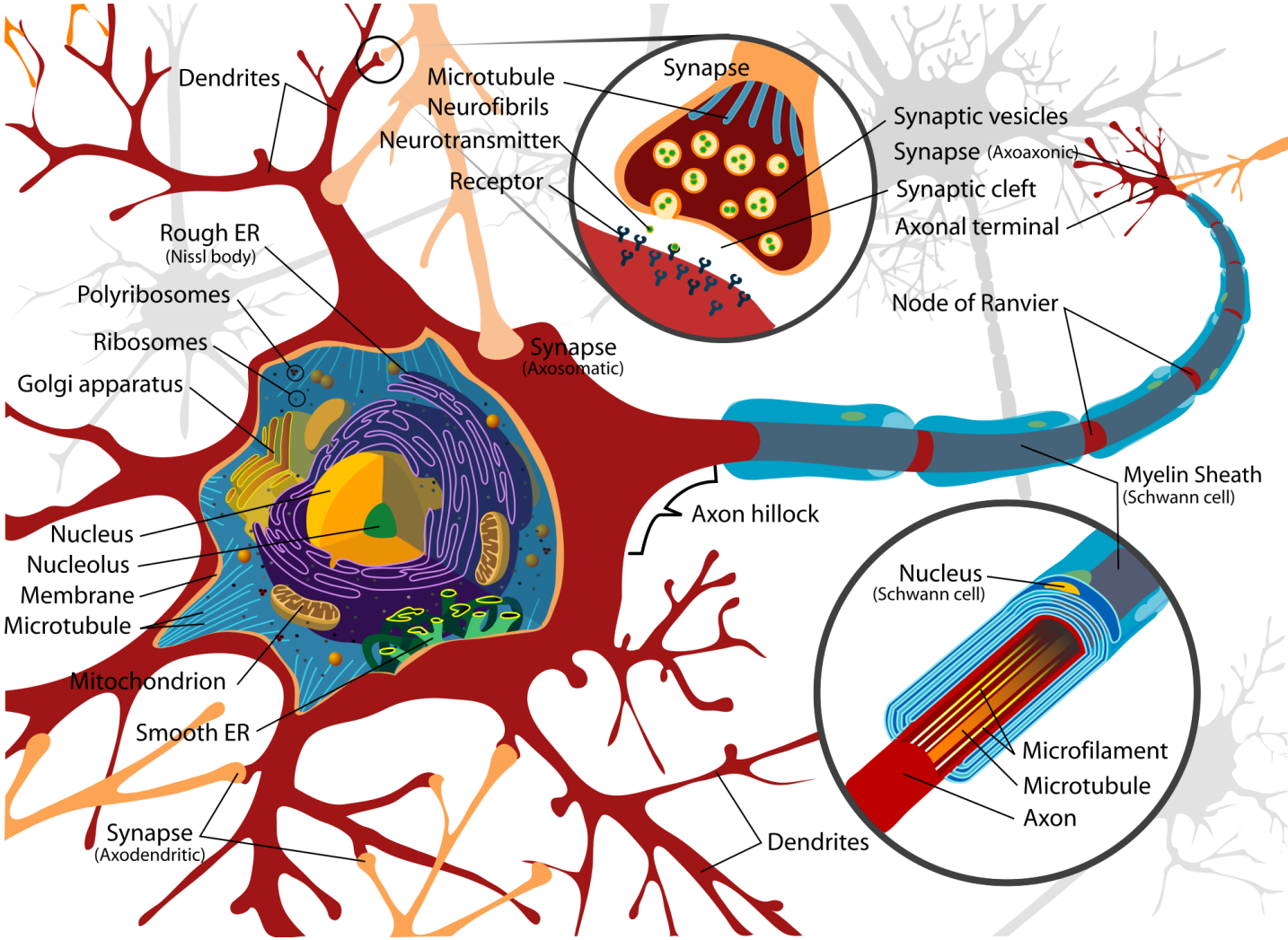
- Free nerve endings:
- Meissner’s corpuscles:
- Pacinian corpuscles:
- Merkel’s discs:
- Ruffini’s corpuscles:
- Muscle spindles:
- Golgi tendon organs:
- Joint receptors:

Neurology – Sensory input

- Free nerve endings: Pain, temperature, crude touch
- Meissner’s corpuscles: Touch, dynamic pressure
- Pacinian corpuscles: Deep pressure, vibration
- Merkel’s discs: Touch, static pressure
- Ruffini’s corpuscles: Skin stretching
- Muscle spindles: Muscle length
- Golgi tendon organs: Muscle tension
- Joint receptors: Joint position

Neurology – Cells





Specialised Glial Cells

- Astrocytes: fill spaces between neurons in brain and are most numerous cell in organ. Mop up chemical messengers that accidentally diffuse into intercellular space to stop signal going to wrong cells.

- Schwann: oligodendroglia, make up myelin – wrap repeatedly around axon to insulate it, speeding up transmission

- Law of dynamic polarisation:

- Law of dynamic polarisation: there is a preferred cell-to-cell direction in which currents move

Neurology - ALS

- What is ALS?

Neurology - ALS

- What is ALS?

- **Amyotrophic lateral sclerosis**

- Lou Gehrig’s disease

Neurology - ALS

- Why is ALS?

Neurology - ALS

- Why is ALS?

- Risk factors – Age (55-75)
  - Men are more likely to develop ALS
  - Caucasians are more likely

Nearly all cases of ALS are considered sporadic

5-10% of ALS cases are familial (C90RF72 gene, SOD1 gene)

Neurology - ALS

- Symptoms of ALS

Neurology - ALS

- Symptoms of ALS

- Muscle twitches
- Muscle cramps
- Spasticity
- Muscle weakness affecting an arm, a leg, the neck, or diagragm
- Slurred speech
- Difficulty chewing or swallowing
- **Symptoms are progressive**

Neurology – ALS Investigations

Neurology – ALS Management

Pharmacological:

Physical and occupational therapy

Neurology – Multiple Sclerosis

- **What is MS?**

Neurology – Multiple Sclerosis

- **What is MS?**

- **Degenerative neuro-inflammatory disease**

- **Cells can also undergo:**
- **Demyelination**
- **Astrogliosis**

Neurology – Multiple Sclerosis

- **Why is MS?**
-

Neurology – Multiple Sclerosis

- **Why is MS?**

Genetic and environmental

Sunlight exposure seems to be a major factor (Vitamin D)

Smoking, Obesity

15% familial recurrence

Immune hypothesis:

- **Increased T lymphocytes in CSF**
- **Increased Ig synthesis in CNS**
- **Entry of T cells into CSF via BBB**
- **Recognise myelin antigens**
- **Destruction of oligodendrocytes by microglia**
- **Plaques most commonly form in the periventricular regions, optic nerves and spinal cord**
- **Gliosis leaves a shrunken, grey, 'silvery' scar**
- **Remyelination occurs, but is not as effective as the original myelin**

Neurology – MS Investigations

Neurology – MS Investigations

- **MRI/CT to detect plaques**
- **● Inflammatory nature confirmed by CSF examination**
- **● Exclusion of other conditions**

Neurology – MS Management

- **Start with monitoring, with no intervention unless 2 significant replases in prior 2 years**
- **Acute - high dose oral steroids**
- **Disease-modifying drugs: β-interferons (largely inactive), cladribine (highly active), natalizumab (rapidly evolving)**

- **Symptom management:**
  - **Spasticity - baclofen, physiotherapy**
  - **Ataxia - isoniazid**
  - **Incontinence - anticholinergics, catheterisation**
  - **Dysaesthesia - carbamazepine**

Why is it important to maintain signalling in the CNS and PNS?

Neurology – Signalling

- Why do we need electrically excitable cells?
- What is electrical excitability?
- What is the ionic make-up of an excitable cell at rest?

Neurology – Signalling

- The movement of ions across a membrane can only occur through
- pumps (active) or channels (passive)
- K+ and negatively-charged proteins are concentrated in the cytoplasm while Na+, Cl- and Ca2+ are amassed in the ECF, giving the interior of cells a net negative charge relative to the outside environment.
- The Na+/K+/ATPase pump is particularly important in maintaining this distribution for biochemical purposes.
- At rest, leak potassium channels are open (these are not voltage dependent) and respond to pH, oxygen potential and mechanical stretch
- At rest, sodium channels are closed

Action Potential

- What is an action potential?

- Action potentials are short pulses of electricity fired when a neurone is stimulated. They are propagated along its length, carrying information.
- The information is encoded in the frequency and patterns of the APs
- The firing rate (not amplitude) shows the intensity of the stimulus
- A sequence of APs shows a long stimulus

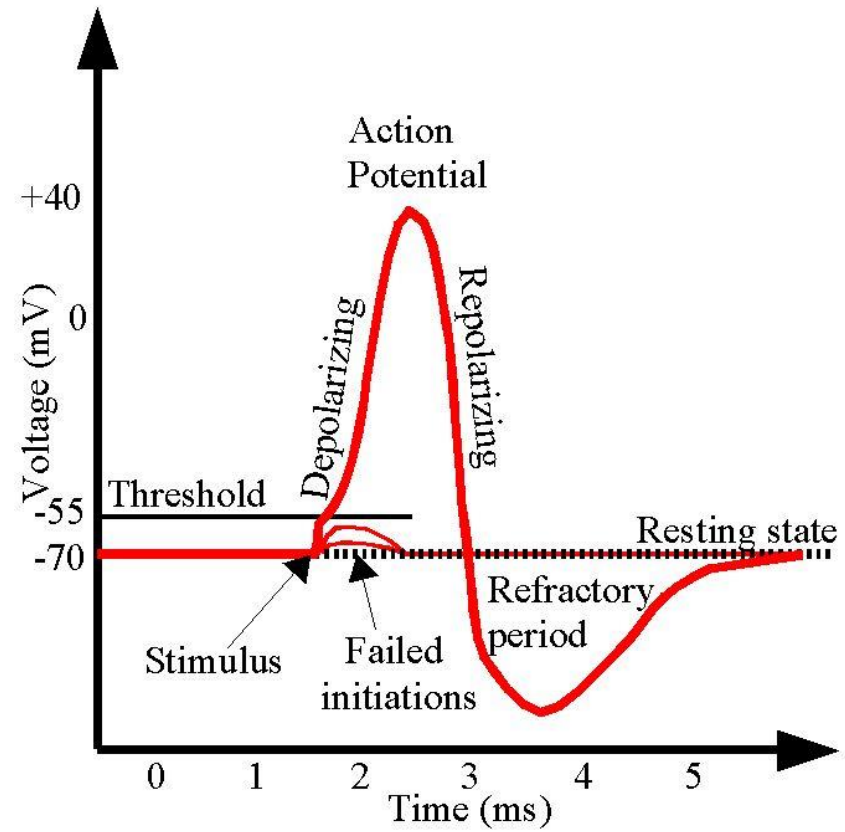
APs give fast, long-range, precise communication (compared to hormonal/chemical messages)

Action Potential

- How does an action potential happen?

Action Potential

- How does an action potential happen?



Neurology – Signalling

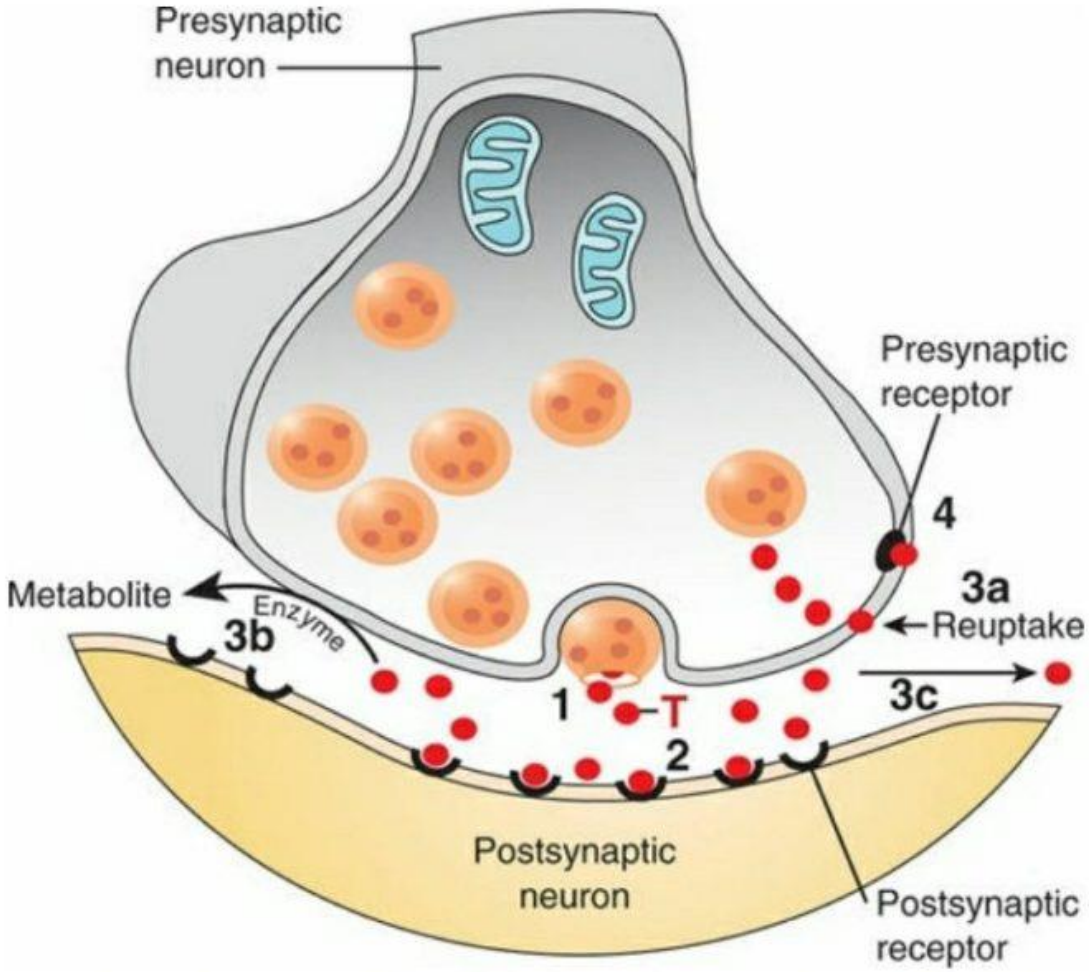
- What are the voltage-gated ion channels?
- What is the difference between the Na+ VGIC and the K+ VGIC?

Neurology – Signalling

- Na+ VGICs are closed at rest to maintain the resting membrane potential
- A stimulus depolarising the membrane to -40mV distorts the protein to open it specifically to Na+ ions
- This rapidly causes much faster depolarisation for 1ms
- The channel inactivates by covering the pore and then closes when the protein returns to its resting configuration after repolarisation of the membrane. The physical pore cover is removed.
- K + VGICs are much slower to open after depolarisation, as entry of K+ resets the membrane potential to resting. During the refractory period after an AP the cell cannot generate another AP, so that depolarisations are discrete.

Neurology – Neurotransmission and Synaptic Control

Neurology – Neurotransmitters



Neurology – Neurotransmitters

- A neurotransmitter is an endogenous chemical messenger that conveys neuronal information from a pre-synaptic terminal to its post-synaptic target. Many different molecules act in this way.
- Enzymes for the synthesis of NTs are produced in the neurone cell body and move down the axon on microtubules
- They produce the NT from precursors in the pre-synaptic terminal, which is then stored in vesicles
- These bind to the cell membrane at the synapse (docking)
- When an action potential reaches the terminal, the membrane is depolarised
- This causes voltage-gated calcium channels to open
- Ca2+ makes the NT vesicles fuse with the membrane (calcium sensing)
- The NT is released into the synaptic cleft (exocytosis)
- It binds to receptors on the post-synaptic neurone
- Enzymes break down the NT and its constituents are taken up into the pre-synaptic terminal for re-use

A new empty vesicle is pinched off the membrane into the pre-synaptic terminal (endocytosis)

- This is filled with NT (loading) for the next AP

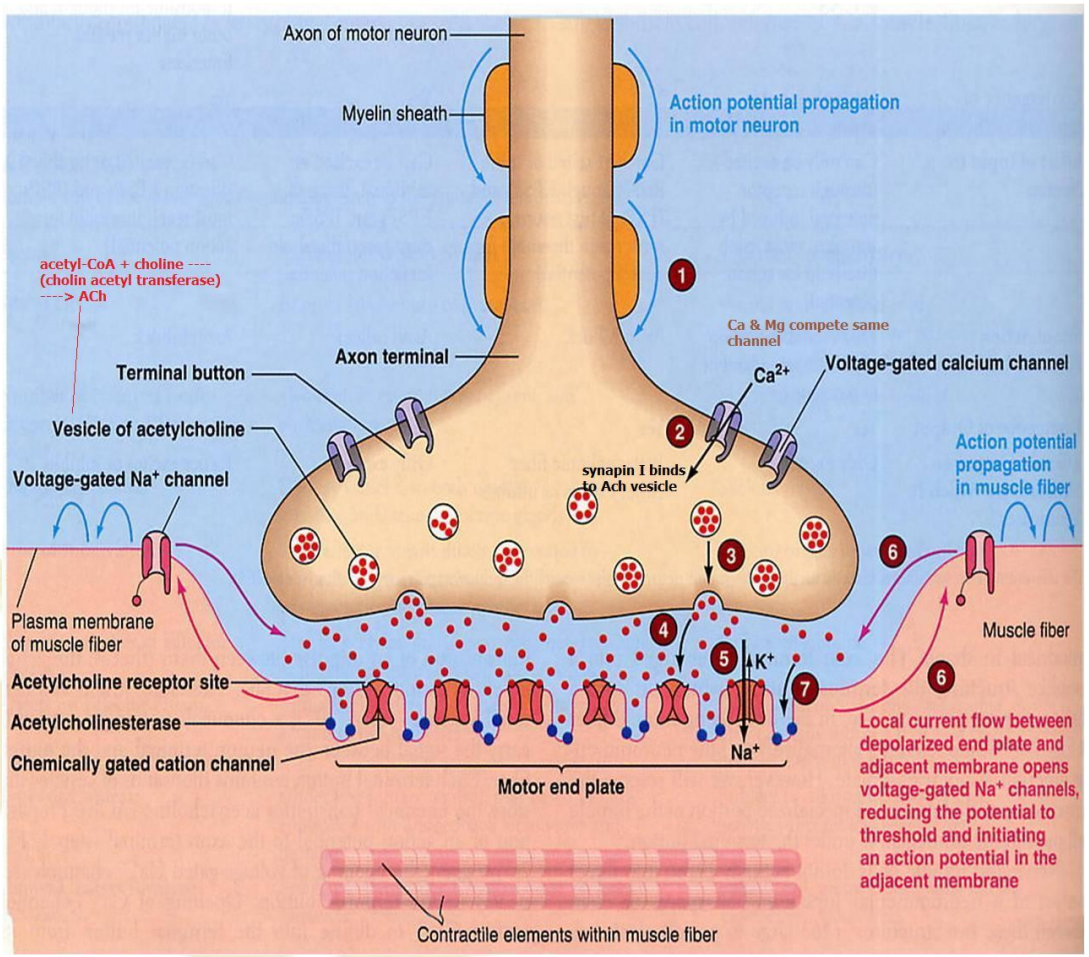
Neurology – Other terms

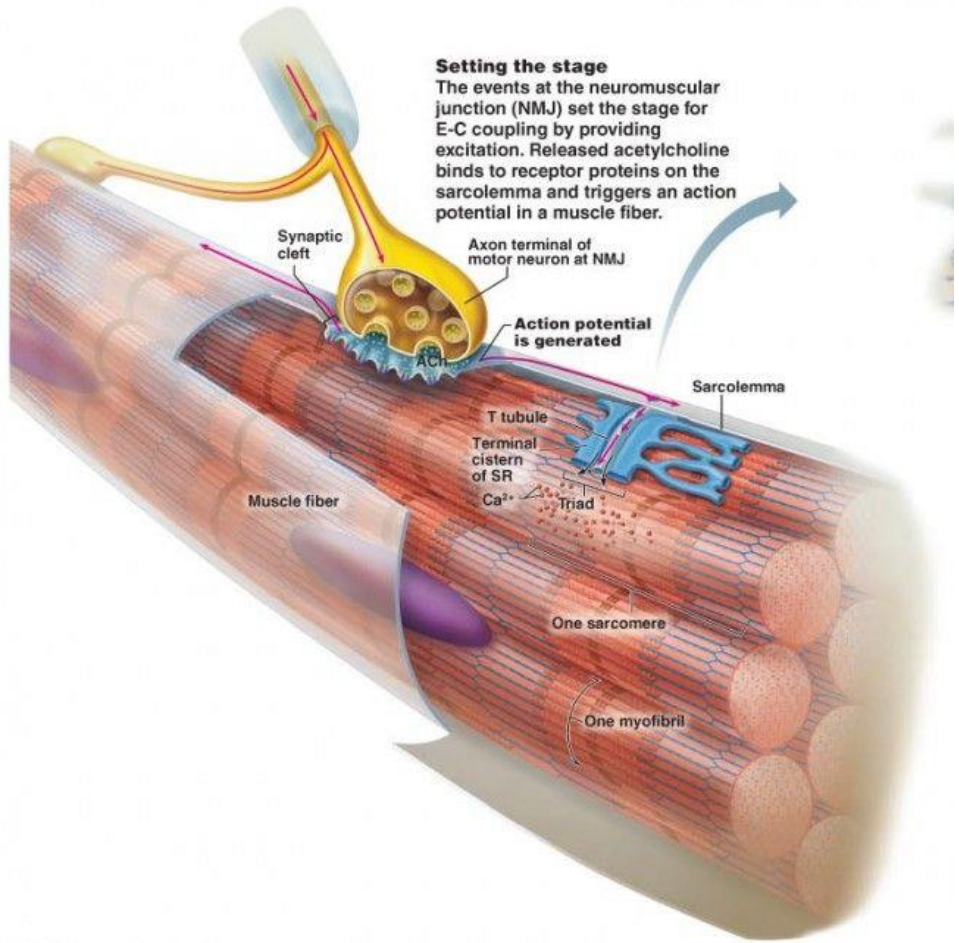
- Ionotropic receptors
- Metabotropic receptors
- Spatial summation
- Temporal summation

Neurology – Other terms

- Ionotropic receptors are fast ligand-gated ion channels that open when the NT bind
- Metabotropic receptors are slow because they activate a second messenger system
- Spatial summation is when a neurone combines multiple EPSPs from different synapse connections
- Temporal summation is when a neurone combines multiple consecutive EPSPs from the same synapse

Neurology – Muscle Contraction - NMJ

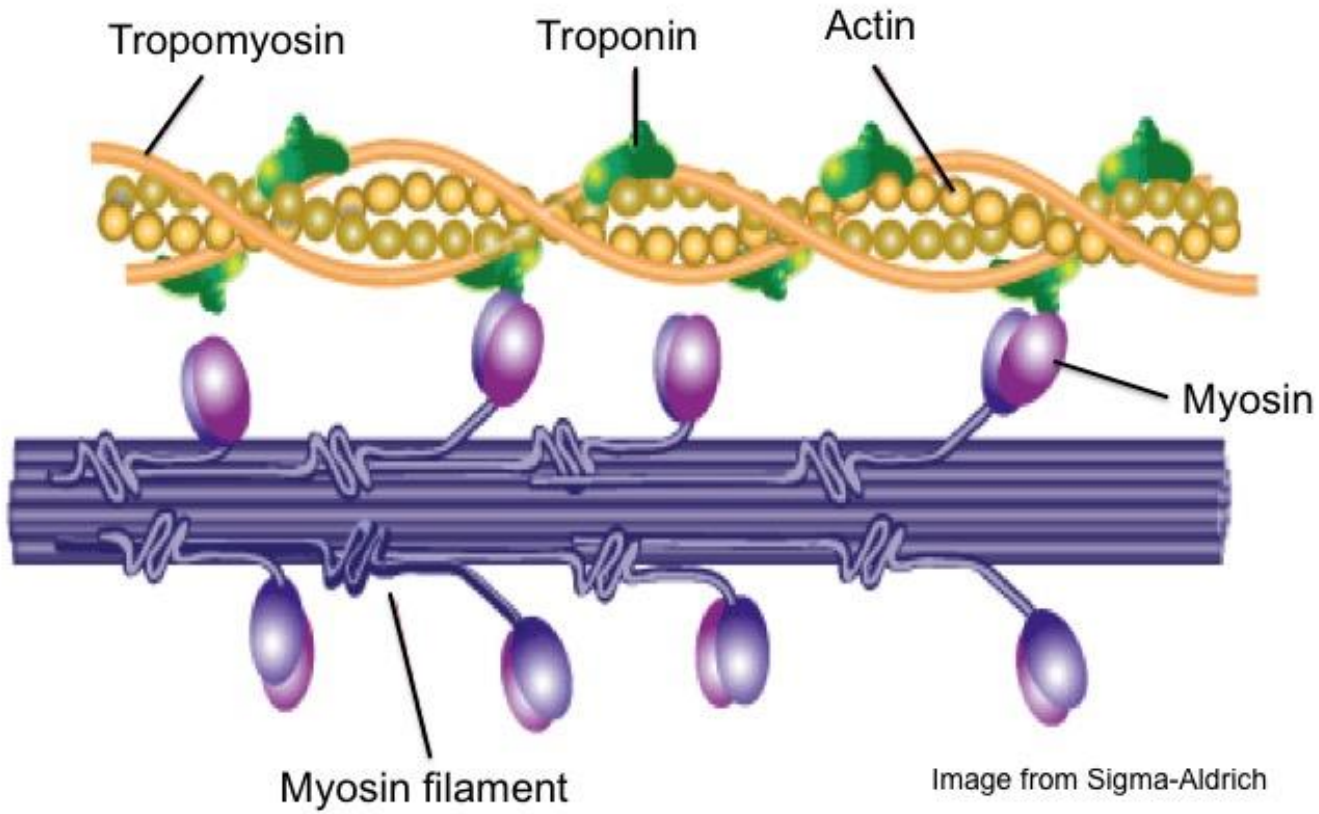




Excitation-Contraction Coupling

- Sarcolemma = excitable cell membrane covering amuscle fibre (one cell) that has infoldings at intervals known as T-tubules
- Sarcoplasmic reticulum = membrane sac storing calcium
- Sarcoplasm = cytoplasm of muscle cell
- Sarcomere = contractile unit between two Z lines

Neurology – Muscle Contraction – Post-Synapse

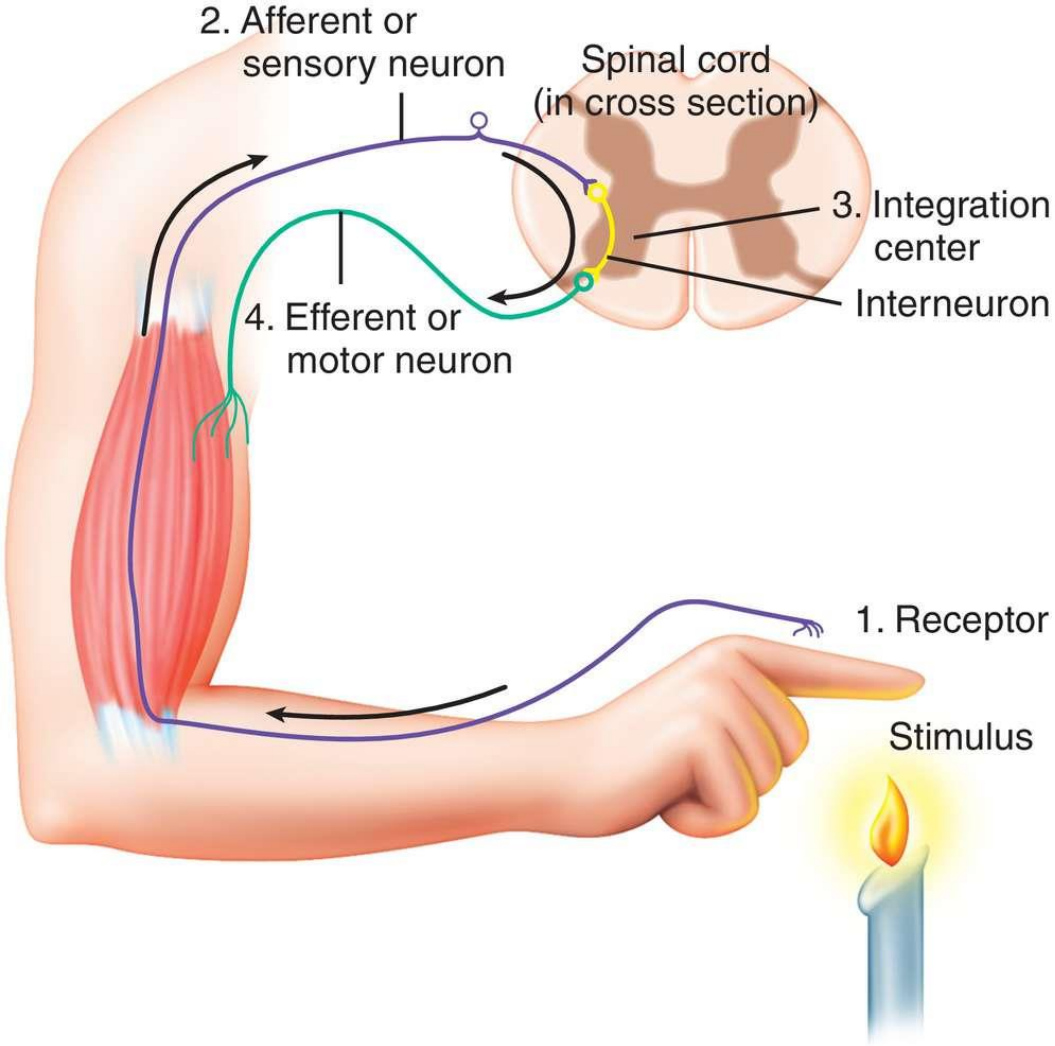


Neurology – Muscle Contraction

- The EPSP generated in the post-synaptic membrane (sarcolemma) travels through the T-tubules (transverse tubules) into the fibre
- This causes the Ca2+ channels of the sarcoplasmic reticulum to open
- Ca2+ diffuses into the sarcoplasm and binds to troponin C so that the myosin heads are free to attach to binding sites on the actin filament
- This binding causes a conformational change in the heads, which pivot and slide the actin filament along the myosin filament to shorten the sarcomere
- ATP is hydrolysed so the head detaches and swings back to its original position, ready to repeat the process for as long as APs and Ca2+ are present

Neurology – Reflex

- Myotatic:
- Crossed extensor:
- • Vestibulo-ocular:



Neurology – Reflex

- Myotatic: in antagonistic pairs of muscles, they are innervated so that one is inhibited when the other is excited to allow movement, e.g. in the knee jerk reflex so that extensors contract and flexors relax
- Crossed extensor: one leg extends when the other flexes, so gives stability when one leg is moved from pain
- Vestibulo-ocular: when the head is rotated, extraocular muscles (around the eyes) are inhibited on one side and excited on the other to fix the position of eyes (and hence line of sight)

Pharmacology

- What is the difference between pharmacodynamics, and pharmacokinetics?

Pharmacology

- What is the difference between pharmacodynamics, and pharmacokinetics?

- Pharmacodynamics is what the drug does to the body. This includes the effects of the drug (both positive and negative), the mechanisms by which they act, and the relationship between concentration and effect.

- Pharmacokinetics is what the body does to a drug. It includes the rate and extent of absorption and distribution, rate and methods of elimination and plasma concentration of drug over time

Pharmacology - Pharmacodynamics

- What are some examples of drug targets?

Pharmacology - Pharmacodynamics

- What are some examples of drug targets?

- Ligand-gated ion channel
- GPCR: target protein is enzyme or channel
- Kinase-linked receptor
- DNA-linked receptor: ligand affects gene transcription
- Enzymes (active site/cofactor)
- Transporters/pumps

Modes of Pharmacodynamic Action

- Agonist:
- Antagonist:
- Partial agonist:
- Inverse agonist:

Modes of Pharmacodynamic Action

- Agonist: drug binds to complementary target protein to induce conformational change in intra-protein bonding, which signals for biological response. Receptors are often named for their principal agonists.
- Antagonist: binds to complementary receptor but causes no change. May be competitive or non-competitive.
- Partial agonist: does not produce a full effect and hence reduces the overall impact of fully saturated receptors.
- Inverse agonist: produces the opposite effect to the agonist by switching off receptors that are constitutively active (by default active without agonist binding). These are very unusual.

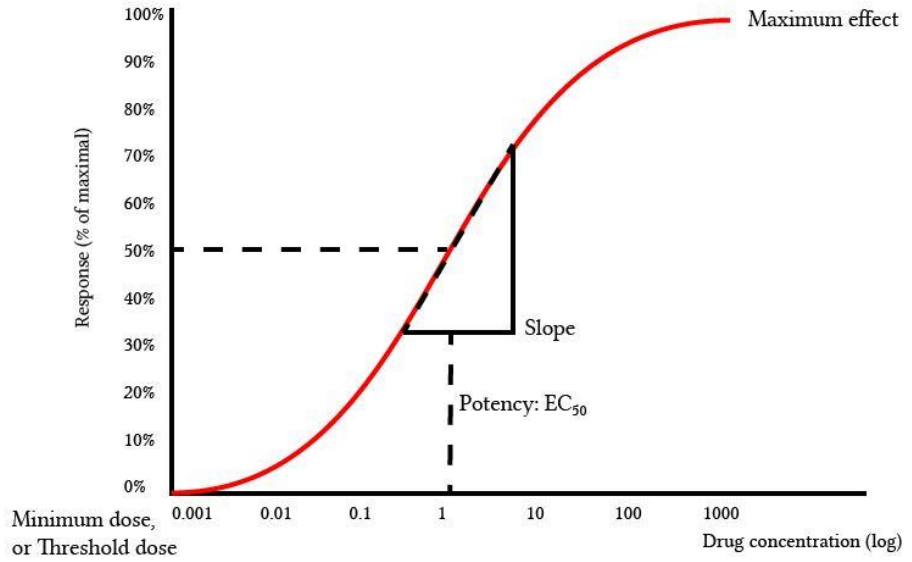
Dose Response Curve

- What is the dose response curve?

Dose Response Curve

- What is the dose response curve?

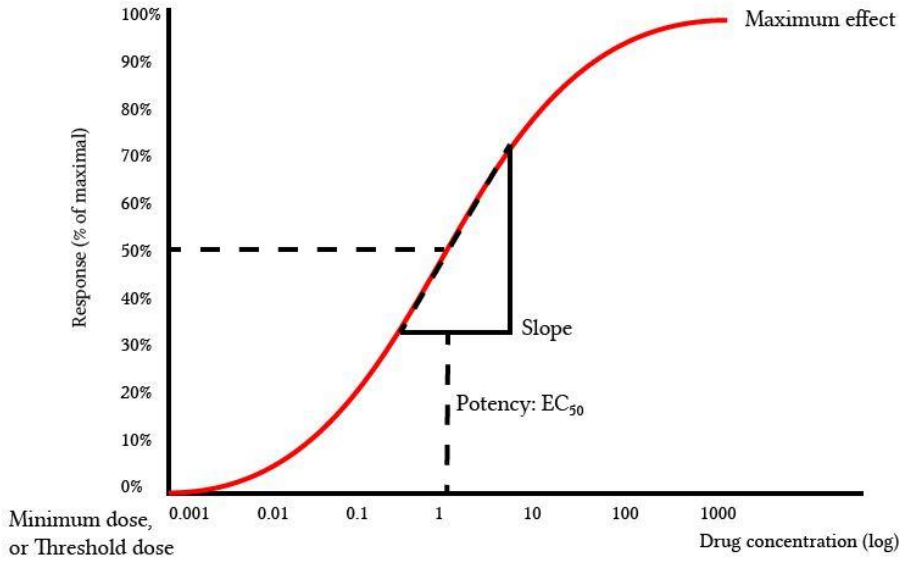
Linear (hyperbolic in shape) or log dose-response graphs can be used to show measured clinical values (the body's biological response to the drug). A log graph (left) will be sigmoidal in shape and shows the effective dose range as the straight region.



Dose Response Curve

- What is the dose response curve?

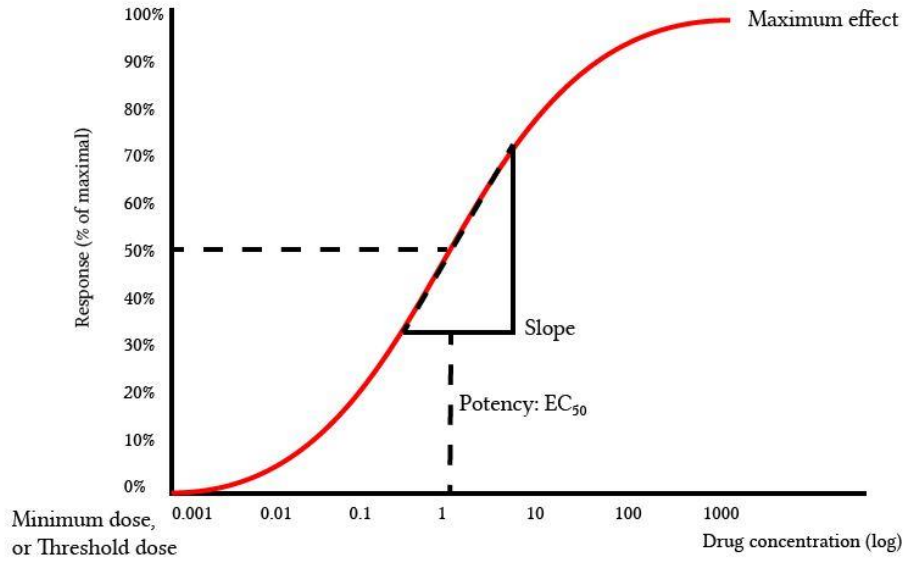
- Emax is the maximum biological response. ED50 is the dose at which 50% of the maximal response is produced.



Dose Response Curve

- How will the following impact the D-R curve?

- Competitive drug antagonists
- Non-competitive drug antagonists
- Partial agonists

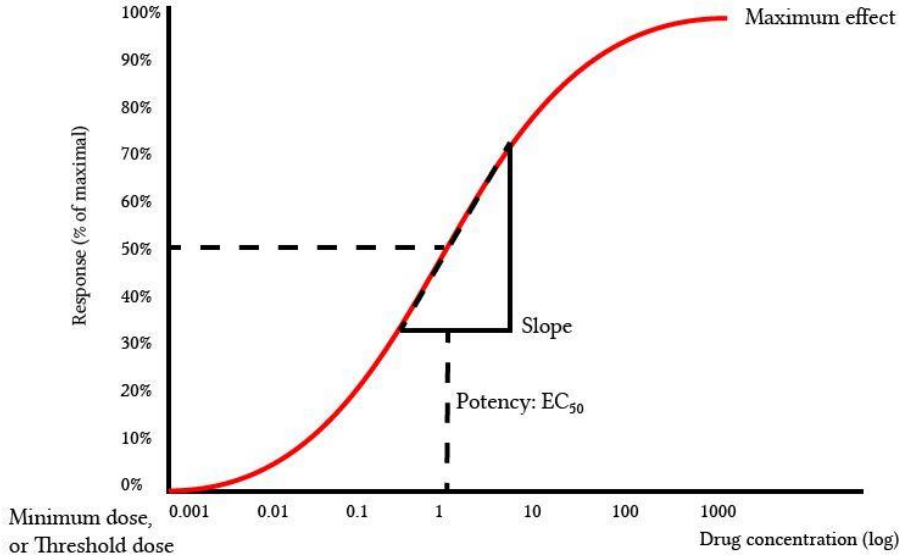


Dose Response Curve

- How will the following impact the D-R curve?

- Competitive drug antagonists will move the D-R curve to the right, as a higher concentration of agonist would be needed to achieve the desired effect. Increased antagonist concentration moves it further to the right.

- Non-competitive drug antagonists move the curve to the right, and also mean that the Emax is reduced - increased drug concentration will not offset the effects of this mechanism, as it does not compete with ligand binding.
- Partial agonists move the curve slightly to the right, but again Emax is not reached as the efficacy is reduced.



More Pharmacodynamics terms

- Affinity
- Efficacy
- Potency

More Pharmacodynamics terms

- The affinity is the strength of the complex between the drug and receptor, dictating how quickly it dissociates. Observing a drug with low affinity for the receptor (e.g. ACh), any changes in drug concentration will quickly be reflected in the level of binding/effects. Therefore, fine control can be carried out by changing the concentration. In drugs with high affinity (e.g. growth hormone), many molecules will be well-bound at a low drug concentration so effects will be prolonged even when the concentration falls.
- The efficacy of a drug is the extent of the response when all receptors are full (Emax). A full agonist will have the greatest efficacy at a receptor whereas a partial agonist will have a lower efficacy. It can also refer to drugs with the same effect but using different mechanisms.
- The potency of a drug is the amount required for a given level of response and is influenced by the affinity. A high potency is not a reason to pick one drug over another – the dosage of a less potent drug can simply be increased.

Desensitisation to Drugs

- What is the difference between tachyphylaxis and tolerance?

Desensitisation to Drugs

- What is the difference between tachyphylaxis and tolerance?

- Tachyphylaxis is fast desensitisation to a drug
- Tolerance is slow desensitisation to drug, usually after prolonged exposure

Pharmacokinetics

- The four categories of pharmacokinetics

- Hint: ADME

Pharmacokinetics

- The four stages of pharmacokinetics

- Hint: ADME

- Absorption
- Distribution
- Metabolism
- Excretion

Absorption – All routes lead to the circulation

- Oral
- IV
- Intramuscular
- Subcutaneous
- Inhaled
- Topical

Distribution

- Vd = D / Co
- Volume of drug distribution = mg of drug givem / mg/l of initial plasma concentration

Distribution

- Vd = D / Co
- Volume of drug distribution = mg of drug givem / mg/l of initial plasma concentration

- The “concentration” of the drug is the free (non-bound) drug present in the fluid compartment of the body – these are blood plasma, interstitial fluid (between cells) and intracellular fluid. The volume of distribution is defined as the total volume of body fluid compartments that the dose has distributed into immediately following IV injection.

Metabolism

- Where does metabolism of a drug largely take place?

Metabolism

- Where does metabolism of a drug largely take place?
- The liver!

Metabolism

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- What does metabolism mean?

Metabolism

- Where does metabolism of a drug largely take place?
- The liver!

- What does metabolism mean?

- Metabolism of a drug (largely in the liver) reduces its bioactivity and increases its water solubility for excretion

Metabolism – Two Phases of Metabolism

- Phase I is oxidation by cytochromes, which can be affected by other drugs (such as warfarin) and makes most drugs inactive.
- Phase II is conjugation, where molecules are added on to make the drug water-soluble. Drug metabolism is affected by a variety of both drug and patient factors, and when it is decreased (such as in cirrhosis), toxic effects or accumulation may occur.

Metabolism – Other Terms

- Interaction:

- First Pass Metabolism:

Metabolism – Other Terms

- Interaction: the presence of one drug affects the metabolism of another. This is by either inducing metabolism via stimulating metabolic liver enzyme production (alcohol, rifampicin) or by inhibiting these enzymes through competition

- First Pass Metabolism: early metabolism of the drug by enzymes in gut wall or liver, which reduces later plasma concentration and possibly body response

Excretion - Routes

Excretion - Routes

- Renal – Eliminated through urine
- Biliary – Enters the bile after liver metabolism
- Lipid soluble drugs/conjugates may be re-absorbed through the gut wall and return to the liver

Excretion - Terms

- Bioavailability: % dose administer that enters the systemic circulation unchanged

- Clearance: Due to metabolism or excretion – the volume of plasma cleared of drug per time either by first order kinetics (constant fraction of drug), or zero order kinetics (constant amount of drug is cleared)

Dosing – Half-life

- Why is half-life of a drug important?

Drugs of the Autonomic Nervous System

- Don’t learn the drug – learn the target, and what happens at the receptor

- α agonists:
- α antagonists:
- β agonists:
- β antagonists:

Drugs of the Neuromuscular Junction

- ACh release blockers: e.g. botulinum toxin. The toxin acts as a protease enzyme on proteins that assist the docking of vesicles containing the neurotransmitter to the pre-synaptic membrane, stopping contraction. The prevention of ACh release can cause muscle paralysis and death, but can also be used cosmetically or to relax muscle spasm.
- Nicotinic ACh receptor blockers: non-depolarising blockers competitively antagonise ACh (cholinergic) receptors to prevent depolarisation in the post-synaptic membrane (sarcolemma). They are based on the natural compound curare and are reversed by anticholinesterase. Can be used as an anaesthetic. Depolarising blockers (Sux is the only one used) agonise the receptor and continue to bind, to keep the ion channel shut. Sux is a dimer of ACh and is broken down slowly by cholinesterase, so has a number of side effects e.g. hypotension and hypothermia.
- Anticholinesterases: prevent the enzymatic breakdown of ACh and so prolong its presence and effects in the NMJ. They are used to diagnose/treat myasthenia gravis (edrophonium, Topic 5), reverse anaesthesia and increase cholinergic activity. Irreversible anticholinesterases are dangerous and can lead to paralysis and cholinergic crisis.
- Muscle relaxants: relieve spasticity by acting in the CNS, PNS or both to block signals for contraction (MS, c. palsy). Dantrolene prevents calcium release from the SR to block contraction, but lack of muscle use can worsen disability