Vertebral Column and Back

Learning Outcomes

- Understand and communicate the key functions of the vertebral column
- Distinguish and differentiate the regions of the vertebral column
- Identify the major anatomical landmarks of a typical vertebra and describe their basic functions
- Differentiate typical cervical, thoracic and lumbar vertebra via distinctive features
    - *Note that thoracic and lumbar vertebral regions will be our primary focus this year*
- Identify and describe the different joints of the vertebral column
- Identify the major vertebral ligaments and the respective landmarks to which they attach
- Identify, name and describe the key muscle groups of the back

Vertebral Column Curvatures

Primary curvatures are 'kyphotic' while secondary curvatures are 'lordotic', with the latter developing in cervical and lumbar regions.

Atypical or Abnormal Curvatures

- Excessive lordosis (lumbar), excessive kyphosis (thoracic), and scoliosis are examples of abnormal curvatures.

Major Anatomical Landmarks of Typical Vertebra

- Vertebral body: weight bearing; articular superiorly and inferiorly; epiphyseal ring
- Arch: pedicles + lamina; forms vertebral foramen; protects spinal cord
- Spinous (directly down) and transverse (sideward) processes: levers for muscles and ligamentous attachment
- Articular processes: projections with articular facets; articulate superiorly and inferiorly; important in synovial joint formation

- As we travel inferiorly along the vertebral column, there is more weight bearing = increase in size of vertical body
    - Thoracic: heart-shaped
    - Lumbar: kidney-shaped
- Cervical vertebrae have transverse foramina and bifid spinal processes
- Thoracic spinous processes projects down (posteriorly and inferiorly) to limit extension
- Lumbar spinal processes are relatively larger
- Sacrum has fused vertebrae

Intervertebral Foramen, Canal, and Notches

- Vertebral foramen: opening in a vertebra through which the spinal cord passes.
- Vertebral canal: passage formed by the vertebral foramen of the vertebrae
- Superior and inferior vertebral notches: indentations on the upper and lower borders of the pedicles of vertebrae, which together form the intervertebral foramina
    - Spinal nerve roots, dorsal root ganglia, and vessels

Intervertebral Joints: Vertebral Body-Disc Joint

- Secondary cartilaginous joint
- Composed of annulus fibrosus and nucleus pulposus
    - Annulus fibrosus: outer layer; attaches to epiphyseal ring; keeps the vertebrae together; concentric lamellae of collagen; permits movement in all directions; resists excessive rotation
    - Nucleus Pulposus: inner layer; keeps the vertebrae apart; gelatinous consistency; shock absorber (disperses compressive forces); deforms but not compressible

Zygopophyseal Joints

- These are plane synovial joints whose movement depends on the orientation of the articular surfaces involved
    - Superior and inferior articular processes have the articular surfaces or (facets)
- The plane of lumbar articular surfaces help with anterior/posterior movement
- The plane of thoracic articular surfaces help with lateral movement and rotation

Major Vertebral Column Ligaments

- Posterior and anterior longitudinal ligaments
- Interspinous ligament
- Supraspinous ligament
- Ligamentum flavum.

Muscles of the Back

- Extrinsic back muscles attach to and act on the upper limb
- Intrinsic back muscles (primarily) attach to and act on the back
    - Erector spinae are the prime movers of the back, particularly in the sagittal plane
        - Concentrically extend the trunk
        - Eccentrically control trunk flexion (eg slowly bending over)
        - Commonly implicated with postural issues
    - Deep to the erector spinae are a group of short muscles collectively known as ‘transversospinalis’

Drugs in the Cardiovascular System - Part Two

Learning Outcomes

- Understand the control of blood pressure, cardiac output and total peripheral resistance
- Understand the use of the following antihypertensive drugs (site of action, mechanisms & adverse effects)
    - α1 -adrenoceptor antagonists
    - angiotensin-converting enzyme inhibitors
    - angiotensin AT1 receptor antagonists
    - Ca2+ channel antagonists

Peripheral Resistance and Blood Pressure

- Anti-hypertensive drugs lower blood pressure by affecting peripheral resistance in blood vessels.
- Poiseuille's Law: resistance is influenced by factors like vessel length, blood viscosity, and vessel diameter

$$Q = \frac{\pi P r^4}{8\eta L} \qquad Q = \frac{P}{R} \qquad R = \frac{8\eta L}{\pi r^4} \qquad R \propto \frac{1}{r^4}$$

Impact of Vessel Diameter on Resistance

- Resistance is inversely proportional to the fourth power of vessel radius.
- Small changes in vessel radius can significantly impact resistance.
- Smaller arteries have a greater effect on total peripheral resistance than larger arteries.

Factors Influencing Vascular Tone

- Passive factors like pressure and vessel structure, and active factors like smooth muscle tone influence resistance.
- Sympathetic nerves release noradrenaline which activate α1 - adrenoceptors on SMC to elicit constriction
- Circulating factors such as catecholamines (adrenaline, noradrenaline), angiotensin II and vasopressin.
- Endothelial cells release vasoactive factors that cause vasodialtion (nitric oxide, prostacyclin) or vasoconstriction (endothelin-1)
- The balance between constrictor and vasodilator factors determines vascular tone.

Hypertension

- TPR is elevated in hypertension and is due to functional imbalance between constriction and relaxation, and structural changes
    - Excessive sympathetic activation, remodelling, or endothelial dysfunction
- As blood pressure rises, blood vessels undergo structural changes (remodelling)
- Vascular remodelling occurs in both primary and secondary hypertension.
- Two major forms of remodelling are inward eutrophic and inward hypertrophic remodelling.
    - Inward eutrophic: rearrangement of smooth muscle cells around a smaller lumen; thicker media; narrower lumen; greater wall thickness:lumen ratio
    - Inward hypertrophy: inward hypertrophy of medial layer encroaches lumen; thicker media, narrower lumen; greater wall thickness:lumen ratio
- Remodelling leads to structural changes that impact vascular resistance and blood pressure regulation.

Consequences of Vascular Remodelling

- Narrowing of the vessel lumen increases vascular resistance at rest.
- Greater media to lumen ratio results in increased resistance and blood pressure in response to constrictor stimuli.

HOW CAN WE LOWER TOTAL PERIPHERAL RESISTANCE?

- By inhibiting sympathetic activation of blood vessels
- By inhibiting the renin-angiotensin system
- By inhibiting signalling pathways involved in smooth muscle contraction

Inhibiting Sympathetic Vasoconstriction

- Targeting vascular alpha one adrenal receptors can inhibit sympathetic vasoconstriction.
- Selective a1 receptor antagonist drugs like prazosin bind to these receptors, leading to vasodilation, decreased peripheral resistance, and lowered blood pressure.
- Adverse effects include:
    - First dose hypotension: excessive fall in BP within 90 min of 1st dose, approx 50% patients
    - Nasal congestion: inhibits α1 -adrenoceptor-mediated constriction of arteries in nasal mucosa; subsequent dilatation leads to nasal congestion.
    - Postural hypotension: fall in BP upon standing, particularly problematic in elderly due to age-related blunting of baroreceptor reflex.
    - Initial reflex tachycardia: baroreceptor reflex - regulates blood pressure by increasing heart rate, contractility, and peripheral resistance when blood pressure falls

Postural Hypotension

- Changes in posture can lead to postural hypotension due to rapid blood pooling in the lower extremities and decreased venous return
- Elderly patients and those on a1 receptor antagonists may have impaired reflex responses.

Inhibiting the Renin-Angiotensin System

- Renin-Angiotensin-Aldosterone system: Angiotensinogen (renin) -> Angiotensin I (Angiotensin-converting enzyme [ACE]) -> Angiotensin II
    - Angiotensinogen is released by juxtaglomerular (granular) cells located in walls of afferent arterioles
    - Renin is released from sympathetic activation of β1-adrenoceptors on granular cells, fall in BP sensed by afferent arteriole, or fall in Na+ delivery to distal renal tubules.
    - Angiotensin I is 40% in lung endothelium, 60% elsewhere
- Angiotensin II plays a key role in vasoconstriction, mediated by AT1 receptors; aldosterone release, mediated by AT1 receptors in adrenal cortex; and cardiovascular remodelling (long-term)
    - Aldosterone secretion leads to increased Na+ and H20 reabsorption
- Renin-angiotensin system inhibitors like ACE inhibitors and AT1 receptor antagonists are commonly used for hypertension.

Comparison of ACE Inhibitors and AT1 Receptor Antagonists

- Both are orally administered
- ACE inhibitors prevent angiotensin II formation and may cause a dry cough due to bradykinin accumulation.
    - Less angiotensin II formation =
        - Less AT1-R mediated vasoconstriction thus lower TPR
        - Less AT1-R mediated aldosterone secretion thus less NA+/H2O retention = lower preload and thus CO leads to lower BP
    - Bradykinin also has minor vasodilative properties = lower TPR and BP
- AT1 receptor antagonists block angiotensin II action and are less likely to cause a cough = higher compliance
- AT1 receptor antagonists are very selective and retain the beneficial effects of angiotensin II on AT2 receptors (counterregulatory role in BP regulation)
- Both classes can reverse pathological cardiovascular changes and have less impact on cardiovascular reflexes.

Advantages and Disadvantages

- ACE inhibitors and AT1 receptor antagonists can cause first dose hypotension, hyperkalaemia (increased in K+ as aldosterone excretes K+), and acute renal failure
    - Hyperkalemia is problematic for patients on K+-sparing diuretics or with renal impairment.
    - Acute renal failure is more problematic in patients with renal artery stenosis where renal function dependent on angiotensin II to maintain glomerular filtration rate, but is reversible
- RAAS inhibitors have advantages like less postural hypertension and safety in asthmatics.
- They can also inhibit cardiovascular remodelling and have a positive impact on structural changes in the heart and vessels.

Impact on Blood Pressure

- Beta blockers primarily impact cardiac output, while alpha-1 adrenergic receptor antagonists lower total peripheral resistance.

Reproductive Physiology

Learning Outcomes

1. Understand the relationship between the hypothalamus, anterior pituitary and peripheral glands in regulating hormone release
    a. The role of negative feedback regulation
    b. The role of positive feedback amplification
2. Explain the role of binding proteins in circulation as important mediators in hormone delivery
3. Identify stages of meiosis as they related to both oogenesis and spermatogenesis
4. Describe the hormonal regulation of spermatogenesis
5. Describe the hormonal regulation of oogenesis
6. Recognize and explain the relationship between the ovarian and uterine cycles

Learning Objective 1: Hormonal Regulation

The relationship between the hypothalamus, anterior pituitary, and peripheral glands is crucial for hormone release regulation. This involves:

- **Negative Feedback Regulation:** A self-regulating system where the stimulus activates a reflex that alleviates the stimulus, restoring balance and signaling to switch off the reflex.
- **Positive Feedback Amplification:** The stimulus enhances the reflex, increasing the signal to drive the reflex and amplifying the response.

Positive feedback cycle during childbirth: it begins when the baby's head pushes against the cervix, triggering stretch receptors. These receptors send signals to the brain, which prompts the release of oxytocin from the posterior pituitary gland. Oxytocin increases the strength and frequency of uterine contractions, further pushing the baby down. As the baby moves further through the birth canal, more stretch receptors are activated, leading to more oxytocin release.

The Hypothalamus and Pituitary Gland

The hypothalamus and pituitary gland work together to regulate hormone release:

- **Posterior Pituitary:** Secretes hormones like oxytocin and antidiuretic hormone (ADH)/ vasopressin into circulation, which were synthesised in the hypothalamus.
- **Anterior Pituitary:** Hormones synthesised in the hypothalamus are released into the hypophyseal portal system and control release of hormone release from the anterior pituitary. Hormones synthesised at the AP are released into circulation to control hormone release from other glands in the body (trophic hormones).

Definitions

- **Tropic/Trophic Hormones:** Hormones secreted by the anterior pituitary that stimulate hormone secretion from other glands (alternative name for stimulating hormones – SH)
- **_trophs:** Cells that secrete trophic hormones (anterior pituitary)
- **_statin:** Inhibiting hormones.
- **Releasing Hormones:** Secreted from the median eminence to stimulate anterior pituitary hormone release.

Thyroid Hormone Regulation

Thyroid hormones are regulated through negative feedback mechanisms, ensuring homeostasis in hormone levels. It begins when the hypothalamus releases thyrotropin-releasing hormone (TRH), which stimulates the pituitary gland to release thyroid-stimulating hormone (TSH). TSH then acts on the thyroid gland, prompting it to produce and release thyroid hormones. These hormones regulate metabolism and other bodily functions. As their levels rise, they inhibit the release of TRH and TSH, preventing overproduction.

Learning Objective 2: Binding Proteins in Hormone Delivery

Hormones can be derived from various sources:

- Amino acids (hydrophilic/hydrophobic)
- Protein hormones (hydrophilic)
- Lipid-derived hormones (hydrophobic) e.g. cholesterols and phospholipids

Lipid soluble molecules cannot dissolve in water. Binding proteins in blood, such as albumin and corticosteroid-binding globulin (CBG), play a crucial role in carrying and circulating hydrophobic hormones. Binding proteins regulate the availability of steroid hormones for receptor binding, with only the unbounded state allowing for hormones to exit circulation and enter the target cell.

Binding proteins found in blood:

- Albumin: abundant; low specificity and low affinity; main role = buffer steroid concentration in blood
- Corticosteroid-binding globulin (CBG): low concentration' high specificity and affinity for glucocorticoids and progesterone
- Sex hormone-binding globulin (SHBG): androgens and oestrogen

Binding proteins can also compartmentalise steroid hormones. In the testes, ABP binds to testosterone, maintaining high local concentrations necessary for spermatogenesis within the seminiferous tubules. By binding the hormone, ABP helps prevent its free diffusion and avoids negative feedback of LH from high levels of systemic testosterone.

Antagonists

Learning Outcomes

- Appreciate the different binding sites of different types of antagonists (competitive, non-competitive, chemical and functional)
- Understand the difference between reversible and irreversible antagonism
- Recognise how different types of antagonists modulate agonist responses
- Understand how partial agonists can act as antagonists
- Have a well-developed understanding of drug selectivity
- Understand aspects of pharmacodynamics and adverse effects which underpin choice of drug dosage

Definition of Antagonists

A molecule that interferes with the interaction of an agonist and a receptor protein or a molecule that blocks the constitutive elevated basal response of a physiological system

Types of Antagonists

- Receptor Antagonists:
    - Competitive antagonist
        - Bind to orthosteric sites
        - Reversible or irreversible
    - Non-competitive antagonist
        - Bind to allosteric site
        - Reversible or irreversible
- Non-receptor Antagonists:
    - Chemical antagonist
    - Functional antagonist

Reversible Competitive Antagonists

- Most common type in labs and clinics due to high potency and selectivity
- Binds to the agonist binding site, termed the orthosteric site, without activating the receptor
    - Prevents agonist from binding to that site
- Does not stay bound to the receptor: dissociates and rebounds continuously.
- e.g. naloxone, an opioid receptor antagonist; treat opioid overdose
- Curve is shifted parallel to the right
    - Apparent potency of the agonist is reduced
- Can be overcome with higher agonist concentrations.

- Who 'wins' the competition for receptor binding depends on

    - concentration of agonist vs antagonist
    - receptor affinity of agonist vs antagonist

- Quantifying antagonism:
    - K_B is the equilibrium dissociation constant of competitive antagonists, a measure of affinity
    - IC_{50} is the concentration of antagonist required to reduce a response to a fixed concentration of agonist by 50%
    - NOTE:
        - IC_{50} is dependent on the concentration of agonist: more agonist requires more antagonist for the same about of inhibition.
        - Inhibition curves say nothing about the type of inhibition (i.e. competitive or non-competitive, reversible or irreversible)

Irreversible Competitive Antagonists

- Bind covalently to agonist sites or dissociated very slowly
- Affects the number of available receptors at a given time point
- At high enough concentration, irreversible competitive antagonists cannot be outcompeted = insurmountable inhibition
- Mainly used as experimental tool with few drugs used clinically
- e.g. phenoxybenzamine: covalently binds to α-adrenoceptors (non-selectively) and block the effects of catecholamines; for treatment of pheochromocytoma

- Rightward shift with increasing concentration
- Maximum reduced: insurmountable
    - May not show reduced maximum if there are spare receptors
        - May need to increase antagonist concentration to see change
- Decreased apparent potency (higher EC_{50})

Partial Agonists as Antagonists

- Can alter the response of an agonist with higher efficacy that binds to the same site
- e.g. buprenorphine: partial opioid receptor agonist; used as analgesic or to reduce opioid withdrawal symptoms
- Acts like a competitive, reversible antagonist: ↓ potency of agonist (higher EC_{50}), surmountable (=E_{max}), rightward shift with increasing concentration
- There is an initial effect of the partial agonist until the full agonist takes over after surpassing the partial agonist concentration

Non-Competitive Antagonist: Allosteric Modulation

- Binds to same receptor but has different binding site to the agonist
- Allosteric modulators influence receptor function by changing receptor conformation.

    - increasing/decreasing the affinity of agonist to orthosteric site
    - increasing/decreasing the efficacy of agonist (including skewing coupling of receptor towards different intracellular signalling pathways, termed biassed agonism)
- e.g. benzodiazepines: positive allosteric modulators of $GABA_A$ receptor (inhibitory transmitter); causes anxiolytic, sedative and anticonvulsant effects

Chemical Antagonists

- Bind directly to or destroy ligands, preventing them from binding to their targets.
- Uncommon among small molecule drugs (e.g. protamine to neutralise heparin; used for cardiac surgery), common for therapeutic antibodies (e.g. mepolizumab, anti-IL-5 antibody; anti-asthma effects)
- e.g. PROTACs (proteolysis-targeting chimeras): bifunctional small-molecules that induce ubiquitin-mediated degradation of target proteins

Functional (Physiological) Antagonists

- Oppose the biological effects of an agonist by acting at a different receptor (as an agonist)
- e.g. salbutamol: agonist at β2-adrenoceptors; causes airway smooth muscle relaxation; treat acute asthmatic attack

Therapeutics

Drug Absorption, Distribution, and Elimination

Dose Determines Effect

Dose is crucial in determining the benefit and risk of a drug, affecting pharmacokinetics, clinical response, and pharmacokinetics.

- Bioavailability
- Volume of Distribution
- Clearance
- Half-life

Pharmacodynamics

Pharmacodynamics is what the drug will do in the body

- Benefit: Desired clinical response (efficacy)
- Risk: Undesired clinical response (toxicity)

Pharmacokinetics

Pharmacokinetics is what the body will do to the drug. It involves drug administration, absorption, distribution, metabolism, and excretion (ADME) to determine dosing. It is also used to determine how much and how often to administer it

- Depends on bioavailability, volume of distribution, clearance, and half-life

Administering the Dose

Drugs can have local or systemic actions based on their administration route.

- Local: administered near; limited tissue access, e.g., skin, lungs, nose, rectum
- Systemic: bloodstream; accesses many tissues, more potential for side effects e.g., oral

Absorption and Drug Properties

Absorption involves how drugs cross membranes, influenced by factors like pH (most are weak acids/bases), aqueous solubility, lipid solubility, and physicochemical properties (size, charge)

- Small (diffusion) vs. Large molecules (pinocytosis)

- Lipid solubility vs pH: acidic/basic drugs are charged/uncharged based on whether it is low/high pH, which impacts their lipid solubility
    - Most drugs are weak acid/bases
    - Uncharged = not lipid soluble = not well absorbed

Systemic Administration

- Oral administration: most common, absorption from the gastrointestinal tract
    - Dose forms: tablets, capsules, powders, solutions
    - pH of GI: stomach 1-3, duodenum 5, small intestine 5-7
        - Usually absorbed through the small intestine
        - Small intestine is superfolded, has villi, microvilli = very large SA
    - Limitations: need to conscious, overdose, compliance, first pass metabolism
    - Saliva enzymes and gastrointestinal fluids: peptides susceptible e.g. insulin
    - Exposed to first pass metabolism
        - Absorbed across portion of GIT that is drained by veins in the hepatoportal system (first pass hepatic metabolism)
            - Nitrates susceptible e.g.
        - Can be used to generate active molecules
            - Prodrugs: e.g. nitrates
- Other routes (parenteral) are used to avoid first pass metabolism
    - Local administration: e.g. skin, lungs, nose, rectum
    - Injectable routes
        - subcutaneous (sc)
        - intramuscular (im)
        - Intradermal (id)
        - intravenous (iv): (need to find vein)
            - instant; exact amount of drug enter blood; no absorption required

Bioavailability and Distribution

Bioavailability (F) determines the proportion of active drugs entering circulation, while distribution involves drug spread in the body.

- Bioavailability affected by absorption (pH, size, lipid solubility), first pass metabolism, and enzyme activity
    - iv = 100% initially, everything else peak <100%
- Distribution is driven by circulation and influenced by molecular size, lipid solubility, **capillary structure,** and **plasma-protein binding** (only free drug has access to tissues)
    - Distribution rarely uniform
    - Once absorbed most drugs distribute rapidly and behave as if in a single compartment
    - Drugs are simultaneously distributing and being eliminated (distribution faster)
        - Reaches distribution equilibrium

Types of Capillaries

Capillaries play a crucial role in drug distribution and absorption in the body. There are three main types of capillaries:

- **Continuous Capillaries:** These have uninterrupted endothelial cells and are found in most tissues. They have intermediate drug accessibility.
    - Brain, eyes, and testes are particularly diffusionally tight, limiting drug entry
- **Fenestrated Capillaries:** Characterised by small pores (fenestrations) that allow for increased permeability, commonly found in the kidneys (drug filtration) and intestines (drug absorption)
- **Sinusoidal Capillaries:** These have larger openings and are found in the liver (drug metabolism) facilitating the exchange of larger molecules.

Binding of Drugs to Plasma Proteins

The binding of drugs to plasma proteins, such as the main one albumin, affects their distribution and elimination. Key factors influencing this binding include:

- Relative affinity of the drug for the protein.
- Amount of protein relative to the drug concentration.
- Drug-drug interactions that may alter binding dynamics.

Free drug access to tissues and elimination processes influence the amount of free drug available, which can be affected by age and disease state.

Specific Binding Proteins

Specific binding proteins exist for several hormones, including:

- Thyroxin binding globulin.
- Corticosteroid binding globulin.

Volume of Distribution

- The volume of distribution is the volume of body water in which a drug appears to be dissolved in after it has distributed throughout the body
- V_d = amount in body/plasma concentration (c_p) = dose given / initial concentration
    - Dose = c_p x V_d x weight
- Volume of distribution is an apparent volume that enables calculation of a starting dose for a drug
- Varies for different drugs based on their properties
    - Tends to be smaller for drugs that bind to plasma proteins; hydrophilic
        - greater concentration appears in plasma
    - Tends to be larger for drugs that distribute to tissues/taken up by cells; lipophilic