

METABOLIC AND ENDOCRINE PHYSIOLOGY AND PHARMACOLOGY

METABOLIC AND ENDOCRINE PHYSIOLOGY

Outline basic cellular physiology in particular
- Structure of the cell membrane and transmembrane transport mechanisms
- Describe the structure of mitochondria. Outline the metabolic processes that occur in the mitochondria: PAST QUESTION
- Composition and regulation of intracellular fluid
- Generation of the trans-membrane potential
- Basic cellular physiology – other
  - Describe the structure and function of voltage sensitive ion channels: PAST QUESTION
  - Describe role of intracellular tight junctions: PAST QUESTION
- What are membrane channels? How are they investigated? Describe one commonly interfered with in anaesthesia: PAST QUESTION
- Describe the mechanism of action of G proteins: PAST QUESTION
- Classify and describe the main intracellular and molecular mechanisms by which chemical neurotransmitters exert their effects. Use acetylcholine and adrenaline neurotransmitters as examples to illustrate: PAST QUESTION
- Energy production by metabolic processes in cells
  - Carbohydrate metabolism
  - Fat metabolism
  - Protein metabolism
  - Electron transport chain
  - Anaerobic metabolism
- Exercise
- Describe the physiological consequences of starvation
  - Compare and contrast the physiological effects of a 6 hour fast of fluids and foods with a 20hr fast in a healthy adult: PAST QUESTION 33%
  - Describe the fuel sources used during early and sustained fasting in man: PAST QUESTION: 51%
  - Hormones involved in regulation of BSL: MAKEUP
- Discuss the factors that influence metabolic rate
- Explain the control of blood glucose
- Describe the physiological consequences of acute hypoglycaemia: PAST QUESTION 57%
- Describe the role of the hypothalamus in the integration of neuro-humoral responses
- Describe control of secretion and the functions of:
  - Pituitary hormones
  - Thyroid hormones
  - Describe the physiological actions of thyroid hormones: PAST QUESTION
  - Thyroid hormone synthesis: MAKEUP
  - Adrenocortical hormones
  - Describe the physiological effects of the glucocorticoids: PAST QUESTION (high fail rate)
  - Outline the physiological effects of bilateral adrenalectomy: PAST QUESTION
  - Adrenomedullary hormones
  - Renin and angiotensin
  - Describe the secretion and function of renin and angiotensin: PAST QUESTION
  - Atrial natriuretic peptide
- Describe the regulation of plasma calcium including the actions and control of vitamin D, parathormone and calcitonin
  - Outline the role of prostaglandins and other autocoids
- Metabolic and endocrine - other
  - Describe sepsis and describe the metabolic consequences of sepsis: PAST QUESTION
  - Outline the components of parenteral nutrition, explaining the rationale for the use of each component: PAST QUESTION 42%
  - Explain how an oxygen debt arises and how the body deals with it: PAST QUESTION 1996
  - Describe the changes that occur with ageing that can affect O2 delivery to the tissues during moderate exercise

ENDOCRINE PHARMACOLOGY

Describe the pharmacology of:
- Insulin preparations
- Oral hypoglycaemics
  - List the main drug groups used in the treatment of diabetes mellitus. For each group explain the mechanism of action and give examples: PAST QUESTION
- Corticosteroid drugs
  - Describe the therapeutic and unwanted effects of dexamethasone: PAST QUESTION
- Outline the pharmacology of:
  - Thyroid hormone replacement and anti-thyroid drugs
  - Glucagon, Vasopressin and analogues
Outline basic cellular physiology in particular

### Structure of the cell membrane and transmembrane transport mechanisms

#### Cell membrane
- **Phospholipid bilayer**
  - hydrophilic (polar) ends outwards
  - hydrophobic (non-polar) fatty acid tail inwards
  - inserted protein channels (transmembrane proteins, peripheral proteins, glucoproteins, glycolipids)
- **Function**
  - Regulates passage of substances between ICF + ECF
  - Prevents passage of water + hydrophilic substances
  - Semi-permeable: different ionic concentrations (and electrical charge) on either side of membrane
- **Functions of CM proteins**
  - Structural
  - Carriers for facilitated diffusion i.e. down EC gradient
  - Pumps for ion active transport
  - Ion channels: diffusion down electro or chemical gradient
  - Receptors: for chemical messengers
  - Enzymes
  - Glycoproteins

#### Transmembrane transport mechanisms

1. **Diffusion**
   - Continual random movement of molecules which relies only on normal kinetic motion of matter
   - **Types of diffusion:**
     i. **Simple diffusion – lipid soluble** (O2, N2, CO2, EtOH)
        - Small, highly soluble lipid molecules dissolve directly in lipid bilayer + diffusion through CM via conc gradient
     ii. **Simple diffusion – lipid insoluble** (H2O)
        - Water crosses CM through aquaporins
     iii. **Diffusion via gated protein channels**
        - Allows passage of charged molecules + exhibits selective permeability due to diameter, shape, electrical charge
          - Voltage gated: e.g. Na, K, Cl; \( \Delta \) shape in response to electrical stimulus (e.g. AP)
          - Chemical/ligand: e.g. ACh, GABA, glycine, NMDA; binding of ligand \( \rightarrow \) open / close
     iv. **Facilitated diffusion**
        - E.g. glucose, amino acids
        - Via carrier protein: binds substrate \( \rightarrow \) conformational change \( \rightarrow \) moves substrate across CM
        - Concentration gradient dependent + limited by amount of carrier protein available
   - Rate of diffusion across CM proportional to:
     - Concentration difference across CM
     - Electrical potential difference
     - Osmotic pressure
     - Carrier protein (for facilitated diffusion)

2. **Active transport**
   - Movement of substances across CM + carrier protein + against EC gradient
   - Relies on kinetic energy + ATP
   - **Types of active transport**
     i. **Primary active transport**
        - E.g. Na/K ATPase pump
        - ATP hydrolysed by carrier protein as it moves substances across CM
     ii. **Secondary active transport**
        - Combination of primary active transport + facilitated diffusion
        - Dependent on energy potential formed by EC gradient set up by primary active transport
        - Classified as:
          - Co transport / symport: both ions move in same direction e.g. SGLT-2
          - Counter transport: ions in opposite directions e.g. Na/K antiporter in CD
   - Factors affecting active transport
     - Concentration difference across CM
     - Electrical potential difference
     - Osmotic pressure
     - Carrier proteins

3. **Other methods**
   - Endocytosis
   - Exocytosis
   - Transytosis

#### Relevant principles:

1. **Gibbs-Donnan effect**
   - If a semi-permeable membrane separates 2 solutions + at least 1 of those solutions contains a non-diffusible ion \( \rightarrow \) the distribution of other ions across the membrane will be altered
   - The distribution of permeable charged ions will be influenced by both their valence + distribution of uncharged ions
   - Important for:
     - Stability of cell vol
     - Plasma oncotic pressure
     - RMP

2. **Fick’s law of diffusion**
Other features of the cell:

1. Nucleus
   a. Function:
      i. site of the cell's genetic material (DNA)
      ii. site of mRNA expression
      iii. regulates functions of organelles through gene expression
   b. contains:
      i. nuclear envelope: double layered membrane that separates nucleus from cytoplasm; passage of selected molecules from cytoplasm to nucleoplasm
      ii. nucleoplasm: gel like substance that surrounds DNA
      iii. nucleolus: site of RNA synthesis

2. Cytoplasm
   a. Portion of cell interior that is not occupied by the nucleus
   b. Contains:
      i. Cytosol (gel like substance)
      ii. Cytoskeleton (protein scaffold that gives shape and support)
      iii. Organelles (small discrete structures that carry out a specific function)

Organelles
- Functional unit of the cell
- Mitochondria
  - Endoplasmic reticulum
    - Protein + lipid synthesising apparatus of the cell
    - Rough ER: site of protein synthesis; contains ribosomes – site where amino acids assembled to form new protein
    - Smooth ER: site of steroid + lipid synthesis; known as SR in muscle cells (intracellular store of Ca2+ that releases Ca2+ following muscle cell membrane depolarisation)
  - Golgi apparatus
    - Modification + packaging of proteins in preparation for secretion
    - Series of tubules stacked alongside ER
      - Modifies proteins: addition of carbohydrate (glycosylation) or phosphate (phosphorylation)
  - Lysosomes
    - Common in phagocytic cells (macrophages and neutrophils)
    - Digestive enzymes, acid, and free radicals
    - Role: destruction of phagocytosed microorganisms

Describe the structure of mitochondria. Outline the metabolic processes that occur in the mitochondria: PAST QUESTION

Mitochondria
Overview
- Generate energy in the form of ATP through aerobic metabolism
- Number present in each cell = proportionate to metabolic activity of cell
- Maternal inheritance (DNA)
- Self replication

Structure
- Contain outer + inner membrane
- Outer membrane:
  - phospholipid bilayer; encloses mitochondria
  - contains porins
  - Intermembrane space: H+ pumped into space by ETC → electrochemical gradient used to synthesise ATP
- Inner membrane:
  - Site of ETC;
  - membrane bound proteins participate in redox reactions → synthesis of ATP
  - Inner mitochondrial matrix = cristae (folds) → site of citric acid cycle, FA metabolism, + urea cycle

Function
- Main function = produce ATP (unit of energy used by cells under aerobic conditions)
- Role in xenobiotic metabolism (role of MAO)
- Steroid hormone synthesis from cholesterol (in adrenal cortex cells)

Production of ATP via the citric acid cycle / oxidative phosphorylation
- Citric acid cycle / Krebs cycle
  - Glucose converted into pyruvic acid via glycolysis → 2 ATP
  - FAs + Aas → acetoacetic acid
  - Pyruvic acid + acetoacetic acid → Acetyl-CoA enters mitochondria
  - Series of reactions results in formation of Co2, 2ATP, electrons in form of H ions bound to intermediate carriers (NAD+, FAD) as NADH + H+ and FADH2
- ETC
  - Electrons transferred from NADH + H+ and FADH2 into ETC → forms energy gradient from high to low potential
  - Energy released from e-s used to pump H+ ions across inner mitochondrial membrane to intermembrane space → creates EC gradient
  - At 3 points, molecular pores allow H+ ions to flow down gradient back into matrix → energy released + used to produce ATP from ADP + phosphate ions (= oxidative phosphorylation)
  - For each molecule of glucose that enters glycolysis, TCA, and oxidative phosphorylation → 38ATP formed (34 in OP)
  - NB oxidative phosphorylation = ETC + chemiosmosis

Composition and regulation of intracellular fluid
Typical RMPs of various cells

**Control of intracellular volume**
- Most CM are freely permeable to H2O → shrink or swell in response to ΔECF tonicity
- However cells maintain a constant volume due to:
  - **1. Intracellular colloid**
    - Intracellular colloid non-diffusible ions (proteins/organic phosphates that cannot cross the CM
    - Intestinal fluid has 4 [protein]
    - NB at equilibrium, electroneutrality would be preserved there is osmolality intracellularity (due to particles) → Intracellular anions would draw water into cell → cell rupture if not counterbalanced.
  - **2. Na/K ATPase + CM low permeability to Na**
    - Counterbalance to prevent cell swell + rupture
    - Na in ECF effectively non-diffusible due to Na/K ATPase pump and Na CM permeability → sets up Gibbs-Donnan equilibrium in opposite direction
    - Gibbs donnan effect due to impermeant extracellular Na balances the Gibbs-Donnan effect due to impermeant intracellular coloids → double-Donnan effect stabilises cell volume

What happens when cells are stressed by a change in ECF tonicity?
- Acute ΔECF tonicity → acute acell volume
  - ΔVolume can have rapid effects on cell vol.
  - Hypertonic ECF → causes cells to shrink: cells 4 in size but partially recover = volume regulatory increase → acutely due to net leak of solute (mostly Na and Cl) into the cell
  - Hypotonic ECF → causes cells to swell: cells swell but then vol 4s towards normal due to volume regulatory decrease → due to loss of intracellular solute esp. K+
- Slow change in tonicity
  - Cells adapt as toxicity is slowly changed - lost or gain solute at a rate which almost matches the effect of change in toxicity
  - E.g. chronic vs. acute hyponatraemia

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

### Neural tissue
- 2 characteristic structural + functional features: excitable membrane, + synapses
- Excitability = ability of neurons to generate + propagate electrical impulses (AP)
- AP = 1 means of communication in nervous system
- 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. The uneven distribution of charge is due 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:
     - Important for maintenance of, and contribution to RMP
     - Conc gradient of ions → EC potential → RMP
     - 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. **Nerst equation**
   - Nerst potential: voltage difference generated by EC gradient of an ion across CM (assuming complete permeability)
   - I.e. describes 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
   - Nerst applied:
     - RMP has †K permeability → net efflux of +vely charged K down conc gradient → drives membrane potential towards Nerst potential for K+
     - RMP †permeability to Na+ ions →
     - Therefore: measured neuronal RMP (~70mM) = close to Nerst potential for K+

2. **Goldman –Hodgkin-Katz equation**
   - Nerst used to calculate membrane potential for single ion
   - Goldman-Hodgkin-Katz equation: considers all ionic permeabilities and concentrations → therefore RMP more precisely quantified

**Gibbs Donnan effect**

**Generation of the trans-membrane potential**

**Typical RMPs of various cells**
Basic cellular physiology – other

Describe the structure and function of voltage sensitive ion channels: PAST QUESTION

**Structure**
- family of transmembrane spanning proteins made up of multiple subunits surrounding a central pore
- opening + closing of pore facilitated by conformational change in subunits dependent on specific changes in membrane voltage
- opening of pore allows movement of ions down their conc gradient

**Function**
- allow propagation/ transduction of electrical signals between cells as a means of rapid communication
- e.g. fast Na channels: arrival of AP to cell (cardiac/ nervous tissue) \(\rightarrow\) Transmembrane voltage - > threshold \(\rightarrow\) channel opens \(\rightarrow\) rapid influx of Na down conc gradient. Once closed CM reverts to RMP

**Examples**
- fast gated Na channels (nerve, cardiac myocyte AP
- L gated Ca2+ channels (cardiac pacemaker AP)

Describe role of intracellular tight junctions: PAST QUESTION

**Tight junctions**

**Structure**:
- tight junctions formed between cells whose membranes fuse to form a barrier to fluid
- occludin proteins + junctional adhesion molecules join cytoskeletons of adjacent cells by forming branching network of sealing strands
- epithelia classified as tight or leaky depending on ability of tight junctions to prevent water and solute movement

**Function**
- hold cells together
- barrier function: protective, functional (prevent passage of molecules/ ions)
- preserves transcellular transport by blocking movement of membrane proteins

**Gap junctions**

**Structure**:
- connect cytoplasm of 2 cells
- 1 gap junction = 2 connexions which connect across intracellular space
- occur in almost all tissues (not RBC)

**Function**
- allow direct electrical communication between cells – esp. important in cardiac
- direct chemical communication between cells via 2nd messengers
- allow passage of molecules <1000 Da. Large biomolecules (proteins) cannot pass

What are membrane channels? How are they investigated? Describe one commonly interfered with in anaesthesia: PAST QUESTION

- membrane channels = proteins that sit in hydrophobic phospholipid bilayer membrane
- create hydrophilic pores that selectively allow passage of ions from one side of membrane to other
- demonstrate selective permeability

**Classification**
- Non gated
  - Aquaporins: allow passage H2O + urea down conc gradient via simple diffusion
  - Gap junctions: low resistance pathway between neighbouring cells; small solutes, ions, H2O can pass down conc gradient
- Voltage gated
  - Transmembrane spanning proteins
  - Made of multiple subunits surrounding a central pore
  - Opening + closing is facilitated by conformational change in subunits dependent on specific changes in membrane voltage
  - 3 states: open, closed, inactive
- Chemical/ ligand gated
  - Binding of another molecule with gate protein causes conformational change in gate protein molecule allowing passage of ions down conc gradient
  - E.g. nAChR, GABA, Glycine, NMDA

**Investigation methods**
- Voltage clamp
  - Using squid giant axons to measure flow of ions through different channels
  - 2 electrodes: 1 measures voltage of membrane; 1 conducts electrical current into/ out of nerve fibre
- patch clamp
  - applying voltage clamp technique to small area of cell membrane using micropipette to try to isolate a small number or one type of channel

**Commonly interfered with in anaesthesia**
- fast Na channel: LA diffuses through membrane (unionised form) \(\rightarrow\) ionise in cytosol and binds to H gate preventing it from leaving inactive state
- nAChR:
  - mostly post synaptic ligand gated cation channel found in NMJ
  - 5 subunit R with central cation pore
  - ACh binds to 2x subunits \(\rightarrow\) conformational change in R \(\rightarrow\) opening of cation pore \(\rightarrow\) influx Na+ / efflux K \(\rightarrow\) depolarisation/ propagation of AP across NMJ
  - Sux = non competitive antagonist (depolarising)
  - NDNMB = competitive

Describe the mechanism of action of G proteins: PAST QUESTION
**G proteins and G protein coupled receptors**

**G proteins**
- Multisubunit protein complex which exchange GDP for GTP in order to bring about an effect
  - GPCR: heterotrimeric G protein (subunits αβγ) with GDP coupled to 7 transmembrane spanning receptor
  - MoA
    - **Activation**: binding of ligand on ECF side of CM → conformational change on cytosolic side → exchange of GDP for GTP
    - **Dissociation**: α-GTP complex dissociates from βγ and interacts with effector proteins
    - **2nd messenger effect**: 2nd messengers then able to activate target proteins (e.g. cAMP or cGMP)
    - **Inactivation**: via intrinsic GTPase activity → results in reformation of α-GDP complex + reassociation with βγ complex
    - **Amplification**: each α-GTP complex is capable of catalysing multiple reactions to form 2nd messengers → amplification pathway
  - Examples of GPCR/α-subunit variability
    - Gs (stimulatory): ↑AC → ↑cAMP → ↑PKA; eg adrenaline, glucagon, PTH, ACTH
    - Gq: ↑PLC → ↑2nd messengers IP3 + DAG → IP3 causes Ca2+ release from ER; DAG activates PKC eg vasopressin, TSH, angiotensin
    - Gi (inhibitory): ↓AC/↓cAMP. E.g. M2 mediated ↓cardiac AP conduction velocity
    - Gt: transducin: molecule responsible for generating signal in the rods of eye in response to light. Gt triggers breakdown of cGMP
  - Targets: G protein can activate (2nd messengers)
    - Adenylyl cyclase or guanylate cyclase → cAMP or cGMP formation
    - Phospholipase C (PLC) on inner surface of CM → catalyse hydrolysis of membrane lipid PIP2 to IP3 or DAG
      - IP3 diffuses to ER where it binds to IP3 receptor (ligand gated Ca channel)
      - DAG stays in cell membrane where it activates protein kinase C

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**Classification of the main intracellular and molecular mechanisms by which chemical neurotransmitters exert their effects. Use acetylcholine and adrenaline neurotransmitters as examples to illustrate:**

See also: section on neurotransmitters

**General:**
- chemical neurotransmission = most common type of synaptic transmission
- NT stored in presynaptic vesicles in nerve terminal
- AP → exocytosis → release of NT into synaptic cleft → diffuse across postsynaptic membrane
- Rs on postsynaptic membrane. Classified as:
  - **Inotropic**: direct action of ion channel → membrane depolarisation / hyperpolarisation
  - **GPCR (metabotropic)**: indirect action on ion channels → changes in K+/Ca2+ conductance via 2nd messengers → depolarisation / hyperpolarisation

**ACh**
- nicotinic (nAChR): 5 subunit R with central cation pore
- classic ionotropic receptor
  - ACh binds 2x subunits → conformational change in receptor → opening of cation pore → influx Na (small Ca influx) / efflux K
- Muscarinic (mAChR): 7 transmembrane spanning domains
  - 5 subtypes
  - M2 (conducting tissue of heart) → ↓AC → ↑K conductance → membrane hyperpolarisation

**Adrenaline**
- α adrenergic receptors
  - α1: ↑PLC (2nd messenger) ↑IP3/DAG → ↑Ca2+ → depolarisation
    - vasoconstriction
    - GI smooth muscle relaxation
    - Salivary secretion
  - α2: ↓AC → ↓cAMP → ↓Ca2+
    - platelet aggregation
    - ↓NA release (presynaptic inhibition)
- βreceptors: ↑AC → ↑cAMP → ↑Ca2+
  - β1: positive inotrope/ chronotrope; relax gastric smooth muscle
  - β2: vasodilation; bronchodilation
  - β3: lipolysis of ↑ brown fat

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**Energy production by metabolic processes in cells**

**Metabolism**
- biochemical reactions that occur within living organisms
- encompasses:
  - Anabolism = building up of larger molecules from smaller ones
  - Catabolism = breaking down into smaller entities with extraction of energy
  - **Cellular respiration**
    1. → series of catabolic processes by which carbohydrates, fats, and proteins are broken down to yield ATP through a series of redox reactions – ultimately using O2 as the oxidising agent.
    2. As O2 is too reactive to be used directly, this process employs a series of intermediate electron carriers, including NAD+ and FAD
  - Catabolism involves a number of processes:
    1. Glycolysis
    2. Lipolysis
    3. Protein catabolism
    4. The citric acid cycle
    5. The electron transport chain
### Carbohydrate metabolism

**Carbohydrate metabolism:**
- glucose = basic unit of carbohydrates
- Active form of glucose = glucose-6-phosphate

**Carbohydrate catabolism:**
Carbohydrates (glucose) can be metabolised by 3 pathways

1. **Glycolysis**
   - glucose converted to 2 molecules of pyruvate + generation of 2 ATP + 2 NADH
   - Occurs in cytoplasm under aerobic + anaerobic conditions
   - 2 ATP molecules used; 4 produced → net gain 2 ATP
   - Steps:
     - 1st step: phosphorylation of glucose → glucose-6-phosphate (via glucokinase)
     - glucose-6-phosphate (6C) → 2 molecules of pyruvate (3C)
     - Fate of pyruvate depends on aerobic or anaerobic conditions:
       - Aerobic: pyruvate into mitochondrion → TCA
       - Anaerobic: pyruvate + NADH → lactate + NAD+
       - If PO2 restored: lactate oxidised back to pyruvate
       - Or lactate oxidized back to pyruvate in liver, or
   - Overall glycolysis reaction: C6H12O6 + NAD+ + 2ADP + 2Pi → 2C3H4O3 + 2NADH + 2ATP

2. **Hexose monophosphate shunt/ pentose phosphate pathway**
   - Produces pentose sugars for nucleic acid synthesis + NADPH for intracellular reduction
   - Does not use ATP or O2
   - Important in liver cells + adipose tissue where it provides energy independent of TCA
   - Overall:
     - NADPH used for fat synthesis from carbohydrates → glucose stored as fat energy
     - H used for oxidative phosphorylation → ATP

3. **The citric acid cycle (tricarboxylic acid cycle “TCA”/ Krebs cycle)**
   - Occurs in inner mitochondrial matrix
   - Cycle of metabolic intermediates producing CO2, ATP + electron donors (NADH + FADH2)
   - O2 not consumed, but cycle cannot operate under anaerobic conditions – this is because ETC FAD for use in citric acid cycle
   - Main substance consumed in TCA = acetyl-CoA; produced from:
     - Pyruvate (from carbohydrate metabolism): pyruvate (3) + CoA-SH + NAD+ → acetyl-CoA + CO2 + NADH
     - B-oxidation of FAs (from fat metabolism)
   - Key features:
     - Acetyl-CoA reacts with oxaloacetate → forms citrate
     - Citrate decarboxylates → gives alpha-ketoglutarate, NADH, CO2
     - Alpha-ketoglutarate decarboxylates reacts with CoA → gives succinyl-CoA, NADH, and CO2
     - Succinyl Co-A undergoes a series of reactions → regenerates oxaloacetate
   - Overall reaction for each acetyl group entering TCA:
     - Acetyl-CoA + 3NAD+ + 3FAD + ADP + Pi + 2H2O → CoA-SH + 3NADH + FADH2 + 3H+ + ATP + 2CO2

**Overall one molecule of glucose yields:**
- anaerobic metabolism = 2 ATP (glycolysis only)
- aerobic metabolism = 36 ATP (glycolysis + TCA + ETC)

### Fat metabolism

**Fat metabolism**
- Lipids involved in body metabolism are obtained from the diet and include:
  - TGs (3FAs + glycerol backbone)
  - Phospholipids
  - Cholesterol
- **Brief note of lipid transport**
  - Digestion: splitting TGs into monoglycerides + FFA
  - Absorption: inside intestinal epithelial cells; resynthesis into TGs + packaged as chylomicrons → circulate in venous system for transport to liver + adipose tissue
  - Storage: lipoprotein lipase hydrolyses TGs + phospholipids in chylomicrons → FFA + glycerol → diffuses into adipose cells + liver (hepatocytes) → resynthesises as TGs inside cells for storage
  - Transport: via synthesised lipoproteins which contain TGs, cholesterol, phospholipids, and protein; formed in liver; transport + deposit lipid components in blood + peripheral tissues. E.g. of lipoproteins – chylomicron, VLDL, LDL, HDL
  - Synthesis: liver can synthesise TGs from carbohydrates; cholesterol + phospholipids from FFAs
  - Mobilisation: stored fat is hydrolysed by hormone sensitive lipase → released + transported as glycerol + FFAs → ionised and carried on albumin. Activation by starvation

**Lipid metabolism**
- FFA
  - catabolised by beta-oxidation in mitochondrial matrix to produce acetyl-CoA
  - involves removing successive 2 carbon units from the FA, each event producing 1 molecule of acetyl-CoA

**NB on hexose monophosphate shunt:**
- Whether glucose-6-phosphate proceeds along the glycolytic pathway or PPP depends on G6PD
  - G6PD = catalyses 1st step of PPP
  - G6PD controlled by cellular concentration of NADP+ → more active if NADP+ levels are ↑
- PPP accounts for 60% of glutathione (antioxidant used to prevent cellular damage from ROS + maintains Hb in ferrous state)
- Pts with G6PD deficiency cannot utilise PPP → loss of reducing power → predisposing pt to MetHb formation
Metabolic and Endocrine Physiology and Pharmacology

Annelise Kerr

Overall this reaction releases: H atoms, NADH, FADH2 (used for oxidative phosphorylation) + acetyl-CoA (enters TCA)

- Ketone bodies:
  - Excess acetyl-CoA forms ketone bodies which recirculate from the liver → diffuse into liver cells + transported to peripheral tissues. Reverse reactions allow further formation of acetyl CoA

Describe the role of insulin in fat metabolism: PAST QUESTION

**Insulin:**
- polypeptide hormone secreted by islet β cells of pancreas in response to ↑BSL
- structure: 2 chains (A chain + B chain) linked by disulphide bridge
- secreted when extracellular Ca²⁺ enters the β cells and binds to calmodulin
- plasma ½ life 5 mins
- anabolic effects on CHO, fat, protein metabolism
- role in fat metabolism = lipogenic (↑glucose uptake and storage) + antilipolytic (↓fat breakdown)

**MoA:**
- binds insulin Rs (tyrosine kinase R) → autophosphorylation → activates 2nd messengers (Shc, IRS) via phosphorylation → alter transcription actors → modulate gene expression → anabolic effects

**Effects on liver**
- ↑glucose uptake, ↑FFA synthesis, ↑glycerol, ↑fat synthesis
  - activates glucokinase
    - phosphorylation of glucose → ↑glucose uptake
    - excess glucose → converted to glycogen (glycogen synthase – activated by insulin)
  - when glycogen store reaches limit (~100g) excess glucose converted to acetyl-CoA (pyruvate dehydrogenase – activated by insulin) → esterified with glycerol to form TGs → stored in liver or released into blood as lipprotein complexes
  - Inhibits ketogenesis

**Effects on adipose tissue**
- ↑glucose uptake, ↑FFA synthesis, ↑glycerol
  - ↑FFA uptake into cells
    - activates lipoprotein lipase: splits TGs in chylomicrons → FFA + glycerol → taken up by fat cells + reconverted back and stored as TGs
    - stimulates GLUT4: ↑glucose uptake in fat cells → form glycerol to further esterify FFA into TGs
  - ↓TG breakdown
    - inhibits hormone sensitive lipase → ↓TGs breakdown → ↑TG storage

**Summary of physiological effects of insulin**
- CHO metabolism
  - ↑glucose uptake / ↑glycogen synthesis
  - ↓glycogenolysis / ↓gluconeogenesis / ↓liver release of glucose into plasma
- protein metabolism
  - ↑aa uptake / ↑aa oxidation
  - ↑protein synthesis / ↓protein breakdown
- fat metabolism
  - ↑glucose entry into adipose tissue
  - ↑clearance of fat in blood (↑LPL)
  - ↑FA synthesis
  - ↑α-glycerophosphate synthesis (backbone for TG synthesis)
  - ↓ketogenesis
  - ↓TG breakdown (↓HSL)
- electrolyte shift
  - ↑membrane permeability to Na → hyperpolarisation → K influx
  - ↑Na/K/ATPase → K influx

**Protein metabolism**

**Protein metabolism**
- NB proteins are only used for energy production if amino acids are plentiful or in starvation
- Inefficient process
- Proteins are 1st broken down into amino acids → to be useful, amino acids must be deaminated. This occurs via:
  1. Oxidative deamination
    - Occurs in liver
    - Catalysed by deaminase enzymes
    - Amino group removed → produces keto acid + NH₃
  2. Transamination
    - amino group transferred (through catalysis by aminotransferases) to a keto acid or other amino acid → to form new amino acid
    - there are 9 essential amino acids that cannot be synthesised by transamination and must be supplied from the diet
    - Keto acid enters TCA → used for energy, transformed into glucose (gluconeogenesis) or used to synthesise another amino acid or FA
    - NH₃ is toxic; it is converted to non-toxic urea by the urea cycle (requires 3 ATP)
**Electron transport chain**

- Final step of carbohydrate, fat, and protein catabolism
- Uses electron donors NADH and FADH2 to produce ATP

**Process:**
- Electrons are transferred from NADH + H+ and FADH2 into the transport chain → forms energy gradient from high to low potential
- Energy released from electrons is used to pump H+ ions across the inner mitochondrial membrane to intermembrane space → creates electrochemical gradient
- At 3 points, molecular pores allow H+ ions to flow down gradient back into the matrix → energy is released → energy used to produce ATP from ADP + phosphate ions (= oxidative phosphorylation)

**Overall:**
- NADH generates 3 ATP molecules
- FADH2 generates 1 ATP molecule

---

**Glucose**

- Glucose comes from 3 main sources:
  - Dietary intake of carbohydrates
  - Breakdown of glycogen in a process called glycogenolysis
  - Generation of glucose from smaller precursor molecules in process gluconeogenesis

- **Glycogen**
  - Glycogen = branched polymer of glucose; major storage form of carbohydrate
  - Production of glycogen stimulated by insulin – which is released as plasma glucose levels ↑ following CHO ingestion
  - **Glycogenesis:**
    - viii. Glucose molecules are phosphorylated by hexokinase in tissue, and glucokinase in liver → glucose-6-phosphate
    - ix. Glucose-6-phosphate converted into glucose-1-phosphate by phosphoglucomutase
    - x. Glucose-1-phosphate molecules are joined together under action of glycogen synthase → glycogen
  - Glycogen stores:
    - xi. Liver: 100g glycogen; skeletal muscle 200g glycogen (cannot be released into circulation; only used by muscle)
    - xii. Glycogenolysis

- **Gluconeogenesis**
  - Energy consuming anabolic process in which glucose is synthesised from non-carbohydrate precursors
  - Importance: one of 2 ways to maintain plasma glucose levels (other is glycogenolysis)
  - Occurs during fasting, starvation, extreme exercise, and low CHO diets
  - Mainly occurs in liver; minor in kidney
  - Substrates: lactate, pyruvate, glycerol, amino acids
  - Separate biochemical pathway – not simply the reverse of glycolysis
  - Glucagon + glucocorticoids promote gluconeogenesis; insulin inhibits it

**Insulin + glucagon**

- resting plasma glucose concentration usually tightly controlled: 3.5-5.5 mmol/L by balance of 2 hormones:
  - 1. Insulin: acts to ↓ plasma glucose concentration (BSL)
  - 2. Glucagon: acts to ↑ BSL

**Insulin**

- Peptide hormone produced in beta cells of Islets of Langerhans in pancreas
- Proinsulin: insulin precursor; A + B chain joined by 2 disulphide bridges + C peptide
- Insulin: formed when C peptide is cleaved by endopeptidases → insulin + free C peptide are packaged in vesicles
- **Exocytosis:**
  - Primary trigger = ↑ BSL
  - ↑ BSL → ↑ facilitated diffusion of glucose through GLUT2 transmembrane channels into B-islet cells → ↑ metabolic activity of cell → ↑ formation of ATP
  - ATP-gated K channels on beta islet cell membrane are closed by ↑ ATP levels → ↓ K flux → membrane depolarisation → triggers opening of voltage gated Ca2+ channels → Ca2+ influx triggers insulin containing vesicle exocytosis
- Plasma insulin secretion occurs in 2 phases:
  - 1. ↑ BSL → rapid ↑ insulin concentration as vesicles with pre-formed insulin empty contents
  - 2. When all vesicles have emptied → B islet cells release insulin as it is synthesised
- **Physiological effects:**
  - 1. Facilitation of glucose uptake: GLUT4 in adipose tissue, skeletal muscle, heart – require insulin to facilitate cellular glucose uptake. NB brain has GLUT-1 and liver has GLUT-2 which are not insulin dependent
  - 2. Storage of metabolic substrates: hepatic glycogenesis, FA synthesis in liver, testification of FAs to make TGs in adipose tissue
  - 3. Inhibition of endogenous glucose production: insulin inhibits lipolysis + glycolysis + gluconeogenesis
  - 4. Cellular uptake of amino acids and K
    - xiii. ↑ amino acid uptake → promotes protein synthesis
    - xiv. 2. ↑ K uptake: prevents hyperkalaemia following meal

**Glucagon**

- peptide hormone produced by alpha cells of islets of Langerhans
- unlike insulin, the have no glucose sensing apparatus
METABOLIC AND ENDOCRINE PHYSIOLOGY AND PHARMACOLOGY

Annelise Kerr

secretion:
- stimulated by hypoglycaemia: hypoglycaemia-induced ↑ANS activity (i.e. indirect) + ↑adrenaline
- inhibited by: insulin, somatostatin, ↑free FA and ketone body concentrations

Actions:
- ↑plasma glucose concentration by:
  - xv. promoting gluconeogenesis
  - xvi. promoting glycogenolysis
  - xvii. inhibiting glycolysis in liver
- Exp. important during starvation

Anaerobic metabolism

Describe the formation, fate, and role of lactate in energy production: PAST QUESTION

- Aerobic conditions: pyruvate passes into mitochondrion → enters citric acid cycle
- Anaerobic conditions: TCA cannot operate → ETC is dependent upon O2 and is needed to regenerate NAD+ and FAD for use in TCA
- lactate = 3C organic acid produced as a result of anaerobic metabolism of pyruvate catalysed by lactate dehydrogenase

Formation of lactate in energy production
- Glycolysis: 9 step series of reactions occurring in cytoplasm: end result = 1 molecule of 6C glucose converted to 2x 3C pyruvate for net gain of 2ATP
- Anaerobic glycolysis:
  - Oxidative phosphorylation ceases: NADH not reoxidised → accumulates: NAD+
  - TCA ceases → acetyl CoA not utilised:
  - Lactic acid fermentation: pyruvate + NADH → lactate + NAD+ via lactate dehydrogenase

Fate of lactate in energy production
- Conversion back to pyruvate
  - When O2 restored: lactate → pyruvate + NADH → able to be utilised by cell that formed the lactate
  - Pyruvate → TCA
  - NAHD → ETC
- Taken up by liver
  - Lactate can be taken up by liver and converted to glucose which may:
  - 1. Enter cori cycle
    - lactate produced by anaerobic glycolysis in muscle moves to liver and is converted to glucose (gluconeogenesis)
    - Shifts metabolic burden from muscle to liver but is not sustainable
    - Important during fasting
    - Lactate produced in muscle cannot be converted to glucose as GLUT4 transporters are unidirectional + G6P not present in muscles
    - In liver: lactate → pyruvate via lactate dehydrogenase (consumes NAD+) → gluconeogenesis → glucose (consumes 6 ATP)
  - 2. Enter TCA to produce ATP
  - 3. Be stored as glycogen
- Diffusion out of cells and transport to heart
  - Cardiac muscle can use lactate as alternate energy substrate

Examiners note: law of mass action was appreciated

Role of lactate in energy production
- Normal serum lactate 0.5-2mmol/L: due to daily production of lactate by cells in low O2 tension environment/ or cells with no mitochondria (RBC, renal medulla, eye) that rely on anaerobic metabolism for energy
- Strenuous exercise: ↑dependence on anaerobic metabolism → ↑lactate
- Anaerobic metabolism: NB glycolysis only sequence of metabolic reactions that does not require O2; not sustainable

Clinical relevance = lactic acidosis
- Lactic acidosis = pH <7.35 + lactate >5mmol/L; common in critically ill patient
- Classified into 2 subtypes:
  - Type A: due to tissue hypoxia – e.g. hypoperfusion
  - Type B: due to non-hypoxic process affecting production + elimination of lactate – e.g. sepsis, hepatic/ renal failure, DM, seizures
- Consequences of lactic acidosis
  - Major adverse consequences which affect all body systems
  - CNS - fatigue, nausea, anorexia, confusion, stupor, coma.
  - CVS - myocardial depression, peripheral vasodilation, decreased catecholamine responsiveness.
  - Resp - Kussmaul's respirations
  - Other - hyperkalaemia, muscle pain

Ketone production
Exercise
- coordinated response to ↑muscle energy needs that involves almost every organ
- energy sources + production in exercise
  - energy for muscle work is derived from breakdown of ATP and creatinine phosphate
  - ATP:
    - Short supply: ATP stored within muscle cell sarcoplasm; 1-2sec
    - Longer supply: myosin ATPase on globular head hydrolyses ATP to release energy to myosin head → form ADP
    - ATP pool small and can only support few contractions → but continuously replenished
  - Creatine phosphate:
    - Converts ADP → ATP
    - 5x size of ATP store → can only sustain max muscle contraction for 8-10s
    - muscle cell replenishes creatinine phosphate pool during recovery by utilising ATP derived from oxidative phosphorylation
  - muscle contraction lasting seconds → mins
    - energy obtained from glycolysis or anaerobic metabolism
    - end products = ATP + lactate
    - lactate: lactate in muscle → converted to pyruvate → oxidised via TCA or
      - Cori cycle: process whereby the liver converts anaerobic metabolic product (lactate) to fuel (glucose)
      - NB glycolysis is inhibited by intracellular acidosis caused by accumulation of lactate
    - Alanine
      - Pyruvate → converted to alanine (non-essential amino acid) → converted to glucose in liver (alanine cycle)
    - Aerobic supply
      - For longer periods of exercise
      - Glucose, FAs, amino acids oxidised in mitochondria to form ATP
      - Muscle glycogen + blood glucose = 50% energy release in active muscle
      - FAs important for prolonged exercise
      - B-oxidation of FAs within mitochondria → acetyl CoA → TCA → ATP

Describe the physiological consequences of starvation

Stavration
- Failure to ingest or absorb sufficient dietary calories to sustain normal body function → resulting in behavioural, physical, metabolic changes
- Major metabolic Δs 2° insulin:glucagon ratio → changes as starvation progresses
- NB: brain + RBC dependent on glucose (can use KB)

3 stages of starvation
- 1. glycogen depletion: 24-48hrs
  - ↓BSL → ↓insulin + ↑glucagon
    - ↑glucagon → glycogenolysis in liver → glycogen store exhausted after 48hrs
    - ↑glucagon + ↓insulin → lipolysis → liberation of FFAs + glycerol from stored TGs
  - ↓ insulin → B oxidation of FFA → ↑acetyl-CoA within mitochondria → ketone bodies
- 2. Protein catabolism: 10-14 days
  - ↑gluconeogenesis: substrates = glycerol, lactate, amino acids
  - ↓plasma insulin → ↑ketone body synthesis
  - Most of protein catabolised comes from liver, spleen, muscle
- 3. Fat metabolism: >14days
  - ↑gluconeogenesis
  - tissues adapt to metabolise ketone bodies; ketones as high as 7mmol/L
  - ↓BMR
  - When fat stores consumed → protein catabolism ↑s → death
  - Other effects: electrolyte disturbances, orthostatic hypotension
  - Death usually from MI, pneumonia (insufficient resp muscle remaining to clear secretions), multi-organ failure

Refeeding syndrome
- severe metabolic disturbance that can occur following reinstitution of nutrition following starvation/ severe malnourishment
- risk if starved >5days
  - onset usually within few days of reinstitution of food
  - features:
    - fluid + electrolyte disorders: ↓PO4, ↓K, ↓Mg, ↑ECF
    - cardiac: tachyarrhythmias, HF
    - neuro: wernicke's encephalopathy, confusion, seizures
  - Mechanism
    - During starvation, ↓plasma insulin → when feeding re-established → ↑BSL → massive ↓insulin secretion by pancreatic Bislet cells →
      - ↑cellular glucose, Mg2+, PO4, K uptake → ↓plasma concentrations
    - ↑BMR + ↑O2 consumption → not well tolerated by cardioesop system stressed by starvation
    - Excessive Na + water retention may precipitate LVF
**Hormones involved in regulation of BSL: MAKEUP**

**Response to 4BSL**

<table>
<thead>
<tr>
<th>Hormone</th>
<th>stimulus</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>4Insulin</td>
<td>4BSL detected by bcells of Iol.</td>
<td>↑glycogenolysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑glycogenesis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑KB (small)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑glucose release</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑glycogenesis</td>
</tr>
</tbody>
</table>

**Liver**

- 4BSL detected by cells of Iol.
- 4insulin
- 4glucagon (peak d4)
- ↑adrenaline
- ↑cortisol
- ↑GH (48h)

**Muscle**

- ↑glycogenolysis
- ↑glucose uptake (via ↓insulin dependent GLUT4)
- ↓TG uptake

**Adipose tissue**

- ↑lipolysis: ↑FFA release
- ↓glucose uptake (via ↓insulin dependent GLUT4)
- ↓TG uptake

**BSL maintained by:**

- Liver:
  - ↑glycogenolysis + ↑glycogen synthesis
- ↑glycogenesis (minor).
  - Cori cycle: liver converts anaerobic metabolic product (lactate) to glucose
  - ↑glucose-alanine cycle: protein degradation = aa (alanine + glutamine)
  - Small amount KB formation
  - Adipose tissue:
    - ↑lipolysis: ↑FFA release
    - ↓glucose uptake (via ↓insulin dependent GLUT4)
    - ↓TG uptake
  - Muscle:
    - ↑glycogenolysis
    - ↓glucose uptake (via ↓insulin dependent GLUT4)
    - ↓protein synthesis
  - Other effects:
    - Previous ingested foods in GIT continue to be absorbed
    - Conservation of body water + maintain circulating vol
- Sustained fasting (24-96h) Gluconeogenic phase
- Sustained fasting >96h Ketogenic phase
- Energy supply mainly from fat → ketone bodies
- Aim: glucose conserved; body uses fat + spares protein; brain + nerves adapt to use ketone bodies; ↓BMR
- Liver: ↑gluconeogenesis

**Adipose tissue: ↑ketogenesis**

- Lipolysis: ↑FFA + ↑glycerol
  - Cori cycle: lactate + pyruvate
  - Muscle: ↑proteolysis → alanine + aa’s
  - 4Adipose tissue: ↑glycerol
  - Muscle: ↑protein catabolism / ↑aa release / 4protein synthesis / ↓glucose uptake
  - Adipose tissue: Lipolysis + ↑FFA + ↑glycerol release
  - Water: 4osmoreceptors + ↑thirst, ADH, SY, RAAS

**NB:** Lipolysis: TG broken down by HSL → ↑FFA / ↑glycerol release → converted to acetylCoA via β-oxidation to enter TCA
### Background

- **Metabolism**
  - Biochemical rxns that occur within living organisms → energy required to sustain life. Involves: anabolism + catabolism
  - Macronutrients involved: CHO, fats, proteins
- **Metabolic rate:** energy output or heat production of a subject per unit time
- **Basal metabolic rate**
  - The amount of energy used per unit time in a subject under standardised conditions at:
    - **Body weight**
    - **Environmental temperature**
    - Fasted for 12 hours
    - In healthy adult = ~70-100 kcal/hr

### Factors that influence metabolic rate

- **Exercise:** muscle exertion → energy consumption (most important)
  - NB role of skeletal muscle as the single largest + most variable source of energy production and therefore the origin of the greatest change in MR
- **Ingestion of food**
  - Dietary induced thermogenesis: energy expenditure during digestion, absorption, and disposal of food
  - Digestion → MR; most due to oxidative deamination in liver
- **Starvation** → ↓MR
- **Temperature**
  - Environmental temp < body temp → activation of heat producing mechanisms → ↑MR
- **Age + growth:** ↓BMR with age; newborn O2 consumption is 7ml/kg/min = 2x adult
- **Body composition:** lean muscle has ↑energy requirement cf fat; ↑body fat % → ↓MR
- **Physiological states:** pregnancy, corticosteroids, catecholamines → ↓MR; sleep → ↓MR
- **Disease states:** malignancy, sepsis, hyperthyroidism → ↑MR
- **Anaesthesia:** GA + MR → ↓muscle activity → ↓MR

### Measurement of BMR = indirect calorimetry

- **Indirect calorimetry** = measures inspired + expired gas flows, vol, and concentrations of O2 + CO2 → determines O2 consumption + CO2 production
- **Principles:**
  - Production of chemical energy is proportional to gas exchange
  - Based on indirect measure of heat produced by oxidation of macronutrients – estimated by monitoring O2 consumption + CO2 production
  - Abbreviated Weir equation used to calculate energy expenditure: REE = \[3.9 \times \text{VO}_2 + 1.1 \times \text{VCO}_2\] × 1.44 (KCal/Day)
- **3 main methods used in indirect calorimetry:**
  - 1. Benedict-Roth spiroometer: simple closed circuit breathing system filled with 6L O2: subject breathes through inspiratory valves → expired air passed into drum through valve and soda lime canister (removes CO2 produced) → as O2 is consumed the vol of drum ↓ and this is recorded. → rate of O2 consumption determined
  - 2. Douglas bag technique: all expired air collected using mouthpiece with insp + exp valves → expired air analysed for O2 and CO2 content → O2 utilisation and CO2 production calculated
  - 3. Max Planck respirometer: based on Douglas Bag method → vol of expired gas measured directly in dry gas meter
- **Errors in indirect calorimetry:**
  - Measures consumption rather than requirements
  - Point estimate of dynamic process

### Explain the control of blood glucose

#### General

- **Normal BSL 4-6mmol/L**
- **Tight BSL control important as:**
  - ↓BSL: disrupt normal function of brain, retina, gonads (obligate glucose users)
  - ↑BSL: ↑osmolality, osmotic load on kidneys → diuresis + cellular dehydration, loss of electrolytes/ substrate → tissue damage

#### BSL control via feedback mechanism

- **Sensors:** pancreatic islets of Langerhans
  - Central regulator: lateral (feeding) and ventromedial (satiety) centres of hypothalamus
- **Effectors**
  - Behavioural (feeding)
  - Hormonal: insulin vs. glucagon balance (act on liver, muscle, adipocytes)
  - Renal (excretion)
  - Modulated by: catecholamines, cortisol, thyroid hormones
    - short term: neuronal mechanisms (SNS activation) + hormones (cortisol, GH)

#### Sensors

- **Pancreatic beta cells** → sense ↑BSL
  - Secrete insulin in biphasic pattern: initial rapid ↑ → prolonged slow ↑
  - **1st phase of insulin secretion:** ↑BSL → glucose enters via GLUT2 → converted to pyruvate → enters TCA → generate ATP → inhibit ATP sensitive K channel → ↓K efflux → depolarisation → open voltage gated Ca2+ channels → exocytosis of insulin granules
- **2nd phase of insulin secretion:** glutamate produced as by-product of TCA → maturation of other insulin granules

#### Effectors

- **insulin:** secreted in response to ↑BSL → following effects to ↓BSL

<table>
<thead>
<tr>
<th>Effectors</th>
<th>Sensory</th>
<th>Action</th>
<th>Body Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>Secreted</td>
<td>Response to ↑BSL</td>
<td>Following effects to ↓BSL</td>
</tr>
</tbody>
</table>
GLUT4 insertion into cell membrane → glucose uptake into cells esp. muscle + fat

- **glucagon**: secreted in response to ↓BSL → following effects to ↑BSL
  - ↑glycogenolysis / ↑gluconeogenesis
  - ↓glycogenesis, ↑glycogen synthesis
  - ↑fat utilisation + ↑protein synthesis

- **Adrenaline**: stimulated by ↓BSL, stress
  - Inhibit insulin
  - Liver: ↓glycogenesis, ↑glucose release, ↑KB
  - Fat: ↑FFA release, ↓glucose uptake
  - Muscle: ↓glucose uptake, ↑FFA metabolism

- Sustained ↓BSL stimulates GH = cortisol release
  - ↑glucose utilisation + ↑fat utilisation → limiting further ↓BSL
  - ↓protein synthesis / ↑aa release / ↑FFA metabolism

2. Neuronal mechanisms
- Hypothalamus directly stimulated by hypoglycaemia → ↑SYNS activity → adrenaline release → stimulates hepatic glucose release

### Physiological response to hypoglycaemia

<table>
<thead>
<tr>
<th>BSL (mmol/L^-1)</th>
<th>Symptoms</th>
<th>Endocrine Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.6</td>
<td>Insulin secretion inhibited</td>
<td></td>
</tr>
<tr>
<td>3.8</td>
<td>Autonomic dysfunction, Glucagon, adrenaline, and GH secretion</td>
<td></td>
</tr>
<tr>
<td>2.8</td>
<td>CNS dysfunction</td>
<td></td>
</tr>
<tr>
<td>2.2</td>
<td>Lethargy, Coma</td>
<td></td>
</tr>
<tr>
<td>1.7</td>
<td>Convulsions</td>
<td></td>
</tr>
<tr>
<td>0.6</td>
<td>Permanent brain damage, Death</td>
<td></td>
</tr>
</tbody>
</table>

**Describe the physiological consequences of acute hypoglycaemia: PAST QUESTION 57%**

- BSL normally maintained 4-7mmol/L
  - maintained by –ve feedback system
    - detector: islets of Langerhans cells in pancreas
    - stimulus= BSL
    - effector = insulin:glucagon release ratio
    - aim: maintain BSL to provide substrate for obligate glucose metabolisers (brain + RBC)
  - hypoglycaemia = BSL <3mmol/L

**Acute hypoglycaemia**
- ↓BSL: compensatory mechanisms not yet activated (hormonal Δs not yet occurred) → glucagon, cortisol, GH levels minimal initial change
  - early sign: hunger
  - later signs: neurological impairment → confusion, agitation → progression with ↓BSL → coma, seizures, death

**Physiological consequences of acute hypoglycaemia**
- **SNS activation** → catecholamine release
  - Central: nausea, agitation, hunger
  - Liver: ↑glycogenolysis, ↑glucose release
  - Pancreas: inhibition of insulin release
  - CVS: ↑HR, ↑TSVR, peripheral shutdown, sweating

- **Insulin release**: ↑BSL detected by βcells of islets of Langerhans
  - adipose tissue:
    - ↓glucose uptake (↓GLUT4 transporters in membrane)
    - ↓fat uptake (extracellular inhibition of LPL in endothelium)
    - ↑FFA release (↑intracellular hormone sensitive lipase)
    - ↑FFA metabolism
  - muscle
    - ↓glucose uptake (↓GLUT4)
    - ↓protein synthesis
    - ↓gluconeogenesis
  - liver
    - ↑glucose release (glycogenolysis)
    - ↑FFA release (some ketone body formation)
    - ↑gluconeogenesis via glycerol (fats) and lactate (RBC metabolism)

- **Catabolic hormones**: ↓BSL stimulates hormonal changes which aim to ↑BSL over sustained period
  - ↑glucagon → ↑hepatic gluconeogenesis from aa, lactate, glycerol
  - cortisol, GH → ↑FFA release from adipose tissue
Describe the role of the hypothalamus in the integration of neuro-humoral responses

**Hypothalamus**
- organ that regulates large number of autonomic/ endocrine processes
- acts as control centre

**Autonomic nervous system activity**
- **CVS:**
  - Ant hypothalamic stimulation $\rightarrow$ ↓BP + ↓HR
  - Post hypothalamic stimulation $\rightarrow$ ↑BP + ↑HR
- Thermoregulatory: integrates thermoreceptor input + controls activity of heat loss + heat gain mechanisms
- Satiety: hunger modulated by glucose, CCK, glucagon, and leptin
- Water balance:
  - Osmoreceptors: control ADH release from posterior pituitary
  - ATII: stimulates thirst + ADH release via subfornical organ + organum vasculosum
- Circadian rhythm
- Behaviour
- Sexual function

**Endocrine/ hormonal activity**
- Direct neural control of posterior pituitary gland
- Pituitary neurosecretory neurons
  - Magnocellular neurons: consists of SON + PVN; synthesise and secrete ADH and oxytocin
  - Parvocellular neurons: form tuberoinfundibular tract $\rightarrow$ secrete hypophysiotropic hormones; release controlled by Nad, dopamine, 5-HT
- Hypothalamic hormones $\rightarrow$ action in pituitary
  - Anterior pituitary by hormone secretion into long portal vein
    - GnRH $\rightarrow$ stimulates FSH + LH release
    - CRH $\rightarrow$ stimulates ACTH release
    - GHRH $\rightarrow$ stimulates GH release
    - TRH $\rightarrow$ stimulates TSH release
    - Somatostatin (GH inhibiting hormone) $\rightarrow$ inhibits GH, TSH, ACTH, and PRL release
    - PRL reseing hormone (PRH): stimulates PRL release
    - Dopamine $\rightarrow$ inhibits PRL release
  - Posterior pituitary by neuronal innervation
    - ACh stimulates release of ADH + oxytoxin
    - NAd inhibits ADH + oxytocin secretion

Describe control of secretion and the functions of:

**Pituitary hormones**

- HPA describes complex feedback loops between these endocrine organs
  - Shortloop feedback: -ve feedback from pituitary on the hypothalamus e.g. thyroxin inhibiting TSH release
  - Long-loop feedback: -ve feedback from pituitary target gland (e.g. thyroid, adrenal, gonads) on the hypothalamus e.g. cortisol inhibiting CRH (as well as ACTH) release
- Pituitary hormones
  - Anterior pituitary
    - Secretes 6 hormones in response to hypothalamic endocrine stimulus
    - Stimulating hormones:
      - Act at another gland
      - Includes: ACTH, TSH, FSH, LH
    - Directly acting hormones
      - Include: GH, prolactin

<table>
<thead>
<tr>
<th>Location</th>
<th>Hormone</th>
<th>Action</th>
<th>Stimulated by:</th>
<th>Inhibited by:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior pituitary</td>
<td>ACTH</td>
<td>Short chain peptide</td>
<td>CRH</td>
<td>Cortisol</td>
</tr>
<tr>
<td></td>
<td>TSH</td>
<td>Glycoprotein</td>
<td>Stimulates synthesis + release of T3 + T4</td>
<td>TRH</td>
</tr>
<tr>
<td></td>
<td>FSH</td>
<td>Glycoprotein gonadotropin</td>
<td>Females: stimulates oestrogen synthesis + ovarian follicle development</td>
<td>GnRH</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Males: stimulates sperm maturation</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>LH</td>
<td>Glycoprotein gonadotropin</td>
<td>Females: rapid 1stimulates ovulation + corpus luteum development</td>
<td>GHRH</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Males: stimulates testosterone synthesis</td>
<td></td>
<td>Somatostatin</td>
</tr>
<tr>
<td></td>
<td>GH</td>
<td>Long chain peptide released in pulsatile fashion</td>
<td>Anabolic effects: directly stimulates lipolysis $\rightarrow$ ↑FFA</td>
<td>IGF-1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Indirectly stimulates IGF-1 release $\rightarrow$ promoting cell growth + development</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Prolactin</td>
<td>Long chain peptide</td>
<td>breast development during gestation + lactation post delivery</td>
<td></td>
</tr>
<tr>
<td>Posterior pituitary</td>
<td>ADH</td>
<td>Short chain peptide</td>
<td>Acts on:</td>
<td>Hypothalamic neural stimulus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>V1 R in vascular smooth muscle $\rightarrow$ vasoconstriction</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>V2 R in CD (↑water reabsorption) + endothelium (↑vWF + FVIII release)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>V3 R in pituitary $\rightarrow$ stimulate ACTH release</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oxytocin</td>
<td>Short chain peptide</td>
<td>structurally similar to ADH</td>
<td>Causes: uterine contraction, let down reflex, psychological, bonding</td>
</tr>
</tbody>
</table>
Thyroid hormones

Describe the physiological actions of thyroid hormones: PAST QUESTION

General
- 3 main thyroid hormones
  - thyroxine (T4): 95%; ½ life 7 days; less active
  - tri-iodothyronine (T3): 7%; ½ life 24hrs; 3-5x activity of T4
  - reverse T3 (rT3): inactive
- T3 + T4 formed from iodination of amino acid tyrosine
- iodine obtained from diet in form of iodide + actively taken up into thyroid follicular cells (req 120-150ug/day)

Release
- TRH from hypothalamus → stimulates TSH release → binds to R on cell membrane of follicular cells, GPCR → cAMP → AC →
  - ↑ iodine uptake into follicular cells
  - ↑ synthesis of T3 + T4 via iodination + ↑ rate coupling reactions
  - ↑ proteolysis of thyroglobulin within follicular cells → liberate T3 + T4
- MoA
  - T3 + T4 highly protein bound (>99%) predominantly to thyroxine binding globulin, albumin, thyroxin binding pre-albumin
  - Thyroid hormones enter cell → T3 binds to intracellular thyroid receptors (TR) → hormone receptor complex = transcription factors (bind to DNA via zinc fingers) → alter gene transcription → clinical effects
  - T4 de-iodinated to T3

Physiological action
<table>
<thead>
<tr>
<th>System</th>
<th>Action</th>
<th>Physiological + pathological effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS</td>
<td>Development</td>
<td>normal CNS development</td>
</tr>
<tr>
<td></td>
<td></td>
<td>retardation, rigidity, deaf-mutism</td>
</tr>
<tr>
<td></td>
<td></td>
<td>sexual function</td>
</tr>
<tr>
<td>CVS</td>
<td>Chronotrope</td>
<td>↑number β-adrenoceptors → ↑HR</td>
</tr>
<tr>
<td></td>
<td>Inotrope</td>
<td>↑cating catecholamines → ↑contractility + ↑CO</td>
</tr>
<tr>
<td></td>
<td>Vasodilation</td>
<td>↑T → ↑body temp → vasodilation → ↓SVR</td>
</tr>
<tr>
<td>Resp</td>
<td>Metabolic</td>
<td>↑T → ↑metabolic rate → ↑MV</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone</td>
<td>Anabolic</td>
<td>essential for normal bone growth</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolic/</td>
<td>Cellular effect</td>
<td>↑Na/K ATPase activity → ↑MR of cells + calorigenic</td>
</tr>
<tr>
<td>endocrine</td>
<td>Feedback</td>
<td>feedback inhibition → ↓TRH + ↓TSH ; ↑T → ↑GH release</td>
</tr>
<tr>
<td></td>
<td>Anabolic/</td>
<td>CHO: ↑TCHO absorption</td>
</tr>
<tr>
<td></td>
<td>catabolic</td>
<td>Fat: ↑lipolysis; ↑LDL Rs → ↑ liver uptake circulating cholesterol</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Protein: physiological amounts: ↑protein synthesis; excess amounts: protein breakdown (thyrotoxic myopathy)</td>
</tr>
</tbody>
</table>

Thyroid hormone synthesis: MAKEUP

Synthesis
- Steps:
  - dietary iodine converted to iodide for absorption
  - iodide actively transported into follicular cells in thyroid (trapping) → oxidised to iodine (via thyroid peroxidase)
  - iodine binds tyrosine in thyroglobulin molecule (iodinase) → forms mono-iodotyrosine and di-iodotyrosine (peroxidase)
  - di-iodotyrosine + di-iodotyrosine = thyroxine (T4) (peroxidase) → binds thyroxine binding globulin + thyroxine binding pre-albumin
  - ↑activity with TSH of:
    - iodide pump activity
    - thyroid peroxidase
    - iodinase
    - peroxidase
    - vesicular lysosomal activity
- thyroid hormones formed within thyroglobulin, synthesised in golgi apparatus
- thyroglobulin stored in follicular colloid → vesicular lysosomal activity breaks down thyroglobulin to release T3 + T4 which diffuse out of follicular cells and into circulation

Metabolism of thyroid hormones
- T4 deiodinated to T3/ rT3 (inactive compound 1:1) → deiodinated in liver, kidney, skeletal muscle to inactive compounds

Negative feedback
### General
- Adrenal glands = paired triangular glands at superior pole of kidney
- Gland divided into: cortex + medulla
- Adrenal cortex
  - 3 layers which produce steroid hormones (mnemonic = GFR layers; ACT hormones)
    - zona glomerulosa → mineralocorticoids (aldosterone)
    - zona fasciculata → glucocorticoids (cortisol, corticosterone)
    - zona reticularis → sex steroids (dehydroepiandrosterone, androstenedione, testosterone)
- Hormones of adrenal cortex = derivatives of cholesterol: contain cyclopentanoperhydrophenanthrene nucleus

### Secrecion
- ACTH binds to high affinity Rs on plasma membrane → activate AC / cAMP / protein kinases → phospholipidated proteins → conversion of cholesterol esters to free cholesterol → pregnenolone (main precursor of cortisol + aldosterone)
- Other effects
  - binding cholesterol to CYP450 in mitochondria
  - uptake LDL from circulation
  - metabolism of phospholipids

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Details</th>
<th>Stimulus</th>
<th>Effect</th>
</tr>
</thead>
</table>
| Aldosterone | 1° mineralocorticoid (95% effect) ½ life 20mins metabolism: liver to tetrahydroglucuronide derivative → excreted in urine regulation: -ve feedback | RAAS: TAlII (↓vol, ↓osmolarity) ↑ACTH ↑[K+] Plasma Na ↓pH | ↑Na+/H2O reabsorption in DCT + CD via...
  - upregulate + activate basolateral Na-KATPase → via MR in principal cells → conc gradient for Na+ reabsorption
  - upregulates apical ENaC → permeability to Na+ ↑reabsorption
  - stimulation of Na/H pump in intercalated cells DCT ↑K excretion |
| Cortisol | 1° glucocorticoid (95% effect) produced at 15-30mg/day diurnal variation: ±morning 90% PB; 75% CBG, 25% alb 10% unbound (active) ½ life 60-90min metabolism: liver; majority reduced to dihydrocortisol → tetrahydrocortisol → conjugated with glucuronic acid → excreted in urine | Stress, ↓BSL, ↑temp → ↑CRH ACTH → cortisol from adrenal cortex | Due to action on genetic mechanism controlling protein synthesis
Stimulating DNA dependent synthesis of specific mrnas in nuclei of target cells → formation of enzymes which alter cellular function
Metabolic: anti-insulin effect → CHO, protein, lipid metabolism
  - Liver: ↑BSL; ↑gluconeogenesis via aa catabolism; ↑glycogenolysis; ↑KB; ↓peripheral utilisation of glucose
  - Muscle: ↑aa release (↑protein catabolism); ↓glucose uptake; ↑FFA metabolism
  - Adipose tissue: ↑lipolysis (↑FFA release; ↓fat storage
  - Overall: ↑plasma glucose, lipid, ketone levels
Anti-inflammatory: immunosuppressive; ↓mast cell degranulation; ↓capillary permeability; ↓effects lymphokines
CNS: excitatory
CVS: ↑contracility, vasoconstriction by ↑number + stimulating action of a1 + b-adrenoceptors
Bone: ↓bone formation / ↓collagen synthesis / ↓OC activity → OP
Haem: ↑RBC / ↓platelets; ↓WCC/cosinophils
GIT: ↓PG synthesis → ↓stress ulceration
Permissive effect: required for glucacon + catecholamines to exert effect
NB glucocorticoids antagonise effects of anticholinesterase drugs |
| Androgens | testosterone = most active androgen | masculinising, ↑protein anabolism, ↑growth androstenedione → oestrogen in peripheral circulation (fat) |

### Physiological effects
- glucocorticoids = steroid hormones released from zona fasciculata in adrenal cortex
- main glucocorticoid = cortisol (95%) + corticosterone (~5%)
- cortisol:
  - synthesised from cholesterol
  - 96% plasma protein bound
  - diurnal variation (peak early morning)
- Regulation
  - HPA + higher inputs from stress and circadian rhythm
  - ↑CRH → ↑ACTH → ↑cortisol

### MoA
- glucocorticoids diffuse into cell → bind cytosolic glucocorticoid Rs → act as transcription factor → alter gene transcription → alter protein synthesis → physiological effects

### Metabolic
  - Liver: ↑BSL; ↑gluconeogenesis via aa catabolism; ↑glycogenolysis; ↑KB; ↓peripheral utilisation of glucose
  - Muscle: ↑aa release (↑protein catabolism); ↓glucose uptake; ↑FFA metabolism
  - Adipose tissue: ↑lipolysis (↑FFA release; ↓fat storage
  - Overall: ↑plasma glucose, lipid, ketone levels

### Anti-inflammatory
  - immunosuppressive; ↓mast cell degranulation; ↓capillary permeability; ↓effects lymphokines

### Effect on foetus
  - Accelerates maturation of lung surfactant
- Permissive effect
  - Small amount of glucocorticoid must be present for other hormones to exert their clinical effects:
  - Required for glucagon + catecholamines to exert calorigenic effects during hypothermia
  - Required for catecholamines to exert vasopressor, lipolytic, bronchodilator effects

---

**Describe the physiological effects of the glucocorticoids:** PAST QUESTION (high fail rate)
Other systems
- CNS: glucocorticoids → irritability + poor concentration
- CV: essential for normal CV response to stress; response to catecholamines (permissive effect) → +ve inotrope
- GIT: 4PG synthesis + faecal production → peptic ulcers
- Renal: handling of body water: 4glucocorticoids → unable to excrete free water load
- Haem: ↑RBC, platelet, neutrophil secretion; eosinophil, basophil, lymphocyte secretion
- Endocrine: inhibits conversion of T4 to active T3; -ve feedback on HPA to inhibit release of CRH

Outline the physiological effects of bilateral adrenalectomy: PAST QUESTION

General:
- Adrenal gland
  - pair of triangular glands situated at superior pole of each kidney
  - responsible for glucocorticoid, mineralocorticoid, and sex steroid synthesis
  - synthesise most adrenaline in body
- B/L adrenalectomy = acute form of "addisonian crisis"

Physiological consequences
- absence of mineralocorticoids (aldosterone)
  - ↓Na reabsorption → ↑Na lost in urine → water loss → dehydration, hypovolaemia, shock, salt wasting crisis
  - K retained in plasma → K secretion
  - Mild acidosis due to lack of H secretion
  - Requires rapid resus + supplementation
- Absence of glucocorticoids (cortisol)
  - ↓BSL 2o
  - gluconeogenesis: impossible to maintain normal BSL
  - weakness
  - ↓mobilisation of protein + fats from tissue
  - highly susceptible to stress + unable to mount stress response
  - effects of catecholamines
- ↓adrenaline
  - ↑ACTH
    - ACTH secretion unopposed due to lack of –ve feedback
    - Severe pigmentation (ACTH stimulates melanin formation)
  - Local effects: headache, visual disturbance

Adrenomedullary hormones
Hormones produced in adrenal medulla = catecholamines:
- adrenaline + noradrenaline
- dopamine

Structure + function of adrenal hormones
- catecholamines all possess catechol nucleus + benzene ring with adjacent hydroxyl substitutions, O-dihydroxybenzene known as catechol
- parent compound = β-phenylethylamine: benzene ring + ethylamine side chain
- optical isomerism conferred by substitution on either of ethyl C atoms
- levorotary substitution at β-C atoms produces naturally occurring NAd + Ad

Biosynthesis of catecholamines
- Synthesis in adrenal medulla (modified SY ganglion composed of chromaffin cells)
- Synthesis + release is dependent on ACh release by presynaptic neuron
- NB catecholamine secretion is not a –ve feedback loop
- Process
  - Tyrosine concentrated in adrenal medulla
  - Tyrosine hydroxylated to DOPA by tyrosine hydroxylase (rate limiting step)
  - DOPA decarboxylated to dopamine
  - Dopamine converted to NAd
  - NAd converted to Ad by PNMT (phenylethanolamine N-methyltransferase)

Stimulus:
- In medulla: CAs are stored bound to ATP in granules with chromogranins
- Release is triggered by an ACh mediated Tintracellular Ca2+ → initiates exocytosis

Function
- CAs act by direct binding to membrane bound receptors
  - α → mobilisation of Ca2+
    - α1:
      - present in smooth muscle
      - Gq coupled
      - PLC → IP3 → Ca2+
      - vasoconstriction, relaxation of GIT mucle
    - α2:
      - present in CNS, arterioles, pancreas
      - Gi coupled
      - Inhibits AC → ↓cAMP
      - vasodilation, sedation, analgesia, inhibition of insulin release
  - β1 + β2 → activation of AC + cAMP
    - β1:
      - cardiac muscle + JGA
      - ↑cAMP → Tintracellular Ca2+
      - inotropy, chronotrophy, dromotropy, renin release
    - β2:
      - skeletal vascular + bronchial smooth muscle, liver, cell membrane
**Renin and angiotensin**

Describe the secretion and function of renin and angiotensin: PAST QUESTION

<table>
<thead>
<tr>
<th>RAAS</th>
<th>- hormone system that regulates BP + water balance in body</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Renin</strong></td>
<td>- acid protease; ½ life 80min</td>
</tr>
<tr>
<td></td>
<td>- released by granular cells in JGA of kidney</td>
</tr>
<tr>
<td></td>
<td>- rate limiting step in RAAS: splits angiotensinogen (produced in liver) to angiotensin I ( \rightarrow ) ATI ( \rightarrow ) ATII by pulmonary ACE</td>
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<td>- Release of renin controlled by:</td>
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<tr>
<td></td>
<td>o SNS</td>
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<tr>
<td></td>
<td>o Intrarenal baroreceptors</td>
</tr>
<tr>
<td></td>
<td>o Macula densa/ tubuloglomerular feedback</td>
</tr>
<tr>
<td></td>
<td>o ATII</td>
</tr>
<tr>
<td></td>
<td>- Factors influencing rate of secretion</td>
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<tr>
<td></td>
<td>o ↑secretion</td>
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</tr>
<tr>
<td><strong>Angiotensin II</strong></td>
<td>- Glycoprotein; ½ life 1-2mins</td>
</tr>
<tr>
<td></td>
<td>- Effector of RAAS</td>
</tr>
<tr>
<td></td>
<td>- Actions via AT1R</td>
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<tr>
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<td>o ↓GFR</td>
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<tr>
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<td>o Vasoconstriction</td>
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</tr>
<tr>
<td></td>
<td>o Tubular absorption</td>
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<td>o central effect</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>o SNS stimulation</td>
</tr>
<tr>
<td></td>
<td>o -ve feedback on renin production</td>
</tr>
</tbody>
</table>

**Problems in anaesthetised pt taking ACEI/ ARBs**

- Hypotension: combination of long duration of action of ACEI/ ARB + anaesthetic agent \( \rightarrow \) ↓BP + potential for CVS collapse
- Angioedema with ACEI 2o bradykinin release
- Renal failure esp. if NSAIDs
- ↑K \( \rightarrow \) risk arrhythmia

**General**

- kidneys play role in regulation of body water + electrolytes
- important component = JGA
- JGA
  o JG cells in wall of afferent arteriole
  | | Involved in pressure regulation through production of adenosine |
  | | Pressure detection: afferent arteriolar baroreceptors |
  | | Effector mechanism: production of renin via granular cells |
- macula densa
  o in walls of distal tubule
  o primary role: tubuloglomerular feedback (autoregulation) through:
    | sensor for flow in DCT |
    | production of locally active vasconstrictor |

**Atrial natriuretic peptide**

<table>
<thead>
<tr>
<th>Production</th>
<th>RA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stimulus</td>
<td>Atrial stretch (TCVP)</td>
</tr>
<tr>
<td>Site of action</td>
<td>Efferent + afferent arteriole CD</td>
</tr>
<tr>
<td>Effect</td>
<td>- dilation afferent arteriole/ constriction efferent arteriole ( \rightarrow ) GFR ( \rightarrow ) H2O, solute filtered.</td>
</tr>
<tr>
<td></td>
<td>- Inhibit RAAS</td>
</tr>
<tr>
<td></td>
<td>- ↓ADH</td>
</tr>
<tr>
<td></td>
<td>- Na absorption proportional to GFR, therefore ↑reabsorption Na ( \rightarrow ) glomerulotubular balance</td>
</tr>
</tbody>
</table>
Describe the regulation of plasma calcium including the actions and control of vitamin D, parathormone and calcitonin

**Functions of Ca²⁺**
- Neuromuscular transmission + nerve function
- Membrane excitation
- Pacemaker potential
- EC coupling + muscle contraction: binds to troponinC, displacing tropomyosin, and exposing binding site for myosin on actin
- Release of hormones and NTs
- Enzyme activation
- Coagulation: activate FVII, VIII, V
- Bone structure
- Intracellular 2nd messenger

**Storage**
- Total Ca²⁺ in body = 400mmol/kg: 99% bone / 1% ICF / 0.3% ECF
- Plasma:
  - 40% protein bound (albumin)
  - 10% chelated to serum anions;
  - 50% free ionised
- ECF Ca²⁺: 2.45-2.55mmol/L / ionized Ca²⁺: 1-1.5mmol/L

**Regulation**

**Absorption**
- daily intake: 1000mg → 10% absorption
- GIT secretes up to 600mg/d → reabsorbed

**Short term regulation = renal reabsorption via PTH + calcitriol**
- large amount filtered by the kidneys; 98-99% reabsorbed
- PT: 60% reabsorbed under control of PTH
- Remainder reabsorbed in asclLoH and DT

**Long term = osteoclast activity via PTH, calcitriol, calcitonin**

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Production</th>
<th>Stimulus</th>
<th>Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PTH</strong></td>
<td>In chief cells of parathyroid Prehormone → cleaved to prohormone → hormone (ER + golgi)</td>
<td>↓[Ca²⁺]</td>
<td>↑Ca²⁺ reabsorption DCT/CD ↓PO4 reabsorption PCT ↑activation of vit D to calcitriol ↑bone resorption/ ↓bone formation → ↑Ca²⁺ release from bone</td>
</tr>
<tr>
<td><strong>Vit D</strong></td>
<td>cholecalciferol (vit D3) produced in skin following exposure to UV light hydroxylated in liver → 25-hydroxycholecalciferol → hydroxylated in prox nephron to 1,25-dihydroxycholecalciferol (calcitriol) (hydroxylase activity dependent on PTH)</td>
<td>↓[Ca²⁺]</td>
<td>↑Ca²⁺ absorption in small intestine ↑bone reabsorption ↑Ca²⁺ + PO4 reabsorption from PCT</td>
</tr>
<tr>
<td><strong>Calcitonin</strong></td>
<td>Secreted from parafollicular cells of thyroid</td>
<td>↑[Ca²⁺]</td>
<td>inhibit osteoblast activity (↓bone reabsorption) ↑Ca/PO4 excretion ↓calcitriol synthesis ↓jejunal absorption of dietary Ca²⁺</td>
</tr>
</tbody>
</table>

**Clinical relevance**
- Hypercalcaemia:
  - <3mmol/L: asymptomatic or non specific sx
  - 3-3.5mmol/L: polyuria, polydipsia, dehydration, anorexia, N+V, weakness
  - CVS: short QT, ↓HR, HTN
- Hypocalcaemia
  - Mild to seizures, heart failure, tetany

**Outline the role of prostaglandins and other autocoids**

Prostaglandins are a series of 20-carbon unsaturated FAs containing cyclopentane ring
- derivatives of arachadonic acid
- not stored; synthesised prior to release
- locally acting autocrine or paracrine messengers

**Synthesis**
- arachadonic acid formed from tissue by phospholipase A2 → converted to prostaglandin H2 (PGH2) by cyclooxygenase 1 (COX1) and COX2
- PGH2 = precursor for other prostaglandins, prostacyclin, and thromboxane via actions of specific enzymes or via free radical oxidation of arachadonic acid

![Prostaglandin receptors](image)
- GPCR named according to class of PG binding to it
- Ligand binding ⇒ stimulates 2nd messengers
- Effects of PGs largely on smooth muscle ⇒ control [Ca2+] ions

**Metabolism**
- local destruction + metabolism of circulating prostaglandins via renal, pulmonary, and hepatic circulations

**Physiological role**

<table>
<thead>
<tr>
<th>Type</th>
<th>Receptor</th>
<th>Physiological Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thromboxane (TXA)</td>
<td>TP</td>
<td>Blood clot activation and stabilization (TXA produced by platelets)</td>
</tr>
<tr>
<td>Prostacyclin (PGI2)</td>
<td>IP1, IP2</td>
<td>Vasodilation (important renal vasodilator) inhibition platelet aggregation (most potent) bronchodilatation</td>
</tr>
<tr>
<td>PGE2</td>
<td>EP1</td>
<td>Bronchoconstriction</td>
</tr>
<tr>
<td></td>
<td>EP2</td>
<td>Bronchodilatation</td>
</tr>
<tr>
<td></td>
<td>EP3</td>
<td>Gastric acid secretion, gastric mucosa secretion, uterus contraction (when pregnant), Gl tract smooth muscle contraction, lipolysis, platelet responses to their agonists and atroventricular block</td>
</tr>
<tr>
<td>Unspecified</td>
<td></td>
<td>Hyporegulation, pyrogenic, Promotes wakefulness</td>
</tr>
<tr>
<td>PGF2a</td>
<td>FP</td>
<td>Uterus contraction, bronchoconstriction, pulmonary vasodilation, vasocostriction, GIT muscle constriction</td>
</tr>
<tr>
<td>PGD2</td>
<td>DP1, DP2</td>
<td>Promotes sleep, renal vasodilator</td>
</tr>
</tbody>
</table>

PGD2, PGE1, PGE2, PGI2 ⇒ oppose vasoconstriction effects of sympathetic nerves or angiotensin II preserving medullary blood flow in high metabolism, low perfusion regions.

**Describe sepsis and describe the metabolic consequences of sepsis:** PAST QUESTION

**Definitions**
- SIRS = systemic inflammatory response syndrome
  - 2 or more of:
    - temp >38 or <36
    - HR >90
    - RR>20
    - WCC>12 or <4
- Sepsis = SIRS + infection
- Severe sepsis = sepsis + haemodynamic instability
- Septic shock = sepsis + end organ dysfunction
- NB spectrum of severity: uncomplicated septicaemia ⇒ sepsis ⇒ severe sepsis ⇒ septic shock

**Systemic consequences of sepsis**
- CNS: 4MAP ⇒ 4cerebral perfusion ⇒ confusion, delirium
- CVS:
  - Bacterial endotoxin ⇒ cytokine release ⇒ vasodilation + ↑vascular permeability ⇒ ↓SVR + ↓MAP + oedema
  - ↓MAP ⇒ baroreceptor ⇒ ↑TNS + ↑HR + ↑TCO
  - inflammatory cytokines ⇒ myocardial depression
- resp
  - ↑metabolic demand ⇒ ↑MV ⇒ ↑RR
  - endothelial dysfunction ⇒ pulmonary interstitial oedema ⇒ V/Q mismatch ↑hypoaemia
  - pulmonary oedema/ ARDS
- GIT: Stress ulcers; ↑gut wall permeability ⇒ ↑migration of bacteria
- Renal: 4MAP ⇒ 4RBF ⇒ 4GFR ⇒ oliguria
- haem
  - Coagulopathic + thrombotic complications
  - DIC
    - activation of coagulation by endothelial damage, endotoxins, immune complexes ⇒ consumption of platelets + coag factors + fibrinolysis
    - blocks microcirculation in organ capillary beds ⇒ cell hypoxia + death
    - platelets + clotting factors unavailable for haemostasis ⇒ "consumption coagulopathy"

**Metabolic consequences**
- hypermetabolic:
  - ↑cytokines ⇒ ↑metabolic rate ⇒ ↑O2 consumption
  - ↑metabolic rate ⇒ ↑thermogenesis ⇒ fever
  - cytokines ⇒ altered hypothalamic temp setpoint ⇒ fever/ rigor
- anaerobic metabolism
  - ↑O2 demand may not be met by resp system ⇒ tissue hypoxia ⇒ ↑anaerobic metabolism ⇒ lactic acidosis
  - hepatic hyperperfusion ⇒ ↓cori cycle ⇒ lactaemia
- catabolism + stress response
  - sepsis ⇒ catabolic state ⇒ depletes stores of glycogen, fat, protein
Effects of ageing

General
Describe the changes that occur with ageing that can affect O2 delivery to the tissues during moderate exercise

How body deals with it:

O2 debt:

General
Explain how an oxygen debt arises and how the body deals with it: PAST QUESTION 1996

Other considerations

Components
Outline the components of parenteral nutrition, explaining the rationale for the use of each component: PAST QUESTION 42%

METABOLIC AND ENDOCRINE PHYSIOLOGY AND PHARMACOLOGY

Cardiovascular
During exercise, O2 delivery can be

O2 flux equation = (Hb x SaO2 x 1.34) + (PaO2 x 0.0003)
O2 flux = amount of O2 delivered to the peripheral tissues per minute
In healthy young adult: tissue O2 delivery = 1L O2/min
O2 flux/ or total body O2 delivery
In healthy young adult: tissue O2 delivery = 1L O2/min
O2 flux = CO x arterial O2 content
In healthy young adult: tissue O2 delivery = 1L O2/min
O2 flux/ or total body O2 delivery
General
- O2 flux = amount of O2 delivered to the peripheral tissues per minute
- O2 flux = CO x arterial O2 content
- In healthy young adult: tissue O2 delivery = 1L O2/min
- O2 flux/ or total body O2 delivery
- O2 flux equation = (Hb x SaO2 x 1.34) + (PaO2 x 0.0003)
- 1.34 = Huffners constant: indicates amount of O2 which can combine with 1g of Hb when fully saturated
- 0.0003 = proportionality constant; represents the amount fo O2 dissolved in blood (Henry’s law) i.e. 0.003ml O2 per mmHg pO2 per decilitre
- During exercise, O2 delivery can be ↑ by:
  - ↑CO globally + locally
  - ↑O2 extraction from tissues

Effects of ageing
- Cardiovascular
  - ▼CO
    - ▼max HR able to be achieved
    - ▼myocardial contractility ➔ ▼SV
    - ↑afterload due to ▼elasticity in large arteries
    - ▼preload due to ▼VR and ▼ventricular compliance
  - ▼cardiac work due to above +/- valve pathology
  - atherosclerosis: ▼blood flow + ▼O2 supply
  - overall: ▼ability to ↑CO to match exercising tissue demands

- β-glucocorticoid + β catecholamines ➔ ↑gluconeogenesis / ↑glycogenolysis / ↑peripheral insulin resistance / ↑lipolysis / ↑protein breakdown
- metabolic acidosis
  - compensation: buffered by HCO3, respiratory compensation, renal compensation

- TPN supplies nutrients IV and is indicated when patients are unable to be fed via the GIT

- Water:
  - Requirement: 30-35ml/kg/day
- Energy in form of CHO + lipids
  - Requirement: 125kg/kg/day
  - Glucose (17kg/g): substrate required by brain + metabolised by all body tissues; prerequisite for protein metabolism
  - Lipids (37kg/g): in form of soybean emulsions; necessary for cell wall integrity + PG synthesis
- Nitrogen in form of aa
  - Requirement: 0.2g/kg/day nitrogen or 1.5g/kg/day amino acids for protein synthesis
- Electrolytes
  - Na+: 1-2mmol/kg/day; nerve conduction + ECF toxicity
  - K+: 0.7-1mmol/kg/day; membrane potential + ICF toxicity
  - Ca2+: 0.1mmol/kg/day: bone metabolism, muscle contraction
  - PO4: 0.7mmol/kg/day: bone metabolism, tissue synthesis, phosphorylation of energy bonds
  - Mg2+: 0.1mmol/kg/day: bone anabolism and enzyme systems
- Vitamins
  - Water soluble: C, B complex group + fat soluble (ADEK)
  - Catalyst or substrate in metabolic reactions
- Trace elements
  - Zinc: constituent of many enzymes e.g. carbonic anhydrase
  - Iron: Hb synthesis
  - Copper: RBC maturation + lipid metabolism
  - Iodine: thyroxine synthesis
  - Others: manganese, gluoride, chromium, selenium

Other considerations
- extra H2O required to replace losses from vomiting, diarrhoea, sweating, fever
- less water required in cardiac/ renal failure
- energy intake supplied primarily as glucose > lipids in liver failure
- energy intake supplied primarily as lipids > glucose in resp failure (↑CO2 production)

Outline the components of parenteral nutrition, explaining the rationale for the use of each component: PAST QUESTION 42%

<table>
<thead>
<tr>
<th>Components</th>
<th>Water:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Requirement: 30-35ml/kg/day</td>
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Other considerations |
| extra H2O required to replace losses from vomiting, diarrhoea, sweating, fever |
| less water required in cardiac/ renal failure |
| energy intake supplied primarily as glucose > lipids in liver failure |
| energy intake supplied primarily as lipids > glucose in resp failure (↑CO2 production) |

EXPLAIN HOW AN OXYGEN DEBT ARISES AND HOW THE BODY DEALS WITH IT: PAST QUESTION 1996

General
- Active tissue utilises ATP for production of energy
- 1st few seconds of vigorous exercise:
  - ATP derived from cellular stores + creatine phosphate (limited stores) + depleted quicklt
- 2nd stage
  - body must switch to substrate metabolism to convert ADP to ATP for energy
  - oxidative phosphorylation within mitochondria (uses CHO, glycogen, FFA)
  - anaerobic metabolism ➔ diversion of glycolytic pathway for production of lactate from CHO

O2 debt:
- during initial stages of exercise, O2 uptake by exercising muscle < max that can be achieved during steady state exercise
- O2 deficit = depletion of cellular ATP, myoglobin O2, and anaerobic metabolism
- As exercise continues ➔ ↑O2 offloading due to R shift OHDC ➔ venous pO2 ➔ maintains O2 requirements for exercise to continue
  - If exercise reaches aerobic threshold ➔ maximal O2 consumption ➔ body commences anaerobic metabolism ➔ lactate
  - How body deals with it:
    - at cessation of exercise: VO2 still ↑ ➔ this is the time that O2 stores are replenished
      - myoglobin replenished
      - creating phosphate/ ATP store replenished

Describe the changes that occur with ageing that can affect O2 delivery to the tissues during moderate exercise

General
- O2 flux = amount of O2 delivered to the peripheral tissues per minute
- O2 flux = CO x arterial O2 content
- In healthy young adult: tissue O2 delivery = 1L O2/min
- O2 flux/ or total body O2 delivery
- O2 flux equation = (Hb x SaO2 x 1.34) + (PaO2 x 0.0003)
- 1.34 = Huffners constant: indicates amount of O2 which can combine with 1g of Hb when fully saturated
- 0.0003 = proportionality constant; represents the amount fo O2 dissolved in blood (Henry’s law) i.e. 0.003ml O2 per mmHg pO2 per decilitre of blood
- During exercise, O2 delivery can be ↑ by:
  - ↑CO globally + locally
  - ↑O2 extraction from tissues

Effects of ageing
- Cardiovascular
  - ▼CO
    - ▼max HR able to be achieved
    - ▼myocardial contractility ➔ ▼SV
    - ↑afterload due to ▼elasticity in large arteries
    - ▼preload due to ▼VR and ▼ventricular compliance
  - ▼cardiac work due to above +/- valve pathology
  - atherosclerosis: ▼blood flow + ▼O2 supply
  - overall: ▼ability to ↑CO to match exercising tissue demands
### Resp

- PaO2: ↓ with age due to ↑ closing capacity; when CC>FRC → airways closure during ventilation → ↑venous admixture → ↓PaO2
- ↓ chest wall compliance
- ↓ diffusion capacity 2o ↑alveolar membrane thickness + ↓functional surface area
- ↑ WOB
- anaemia → ↓ O2 carrying capacity
- overall: ↑V/Q mismatch → ↓ability to oxygenate blood when tissue extraction ↑s
Describe the pharmacology of:

**Insulin preparations**

<table>
<thead>
<tr>
<th>Chem</th>
<th>Uses</th>
<th>Pres</th>
<th>Action</th>
<th>Metabolic</th>
<th>Electrolyte</th>
<th>Toxicity/ SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naturally occurring: polypeptide hormone; synthesised from proinsulin in rough ER of β cells</td>
<td>DM BSL control, hyperkalaemia BB/CCB toxicity</td>
<td>CSI for injection typically 100U/ml</td>
<td>Stimulation of CHO metabolism, protein synthesis, lipogenesis binds to + activates specific membrane bound R → effects mediated by alterations in intracellular concentrations of cyclic nucleotides</td>
<td>- Liver ○ ↑ rate of diffusion of glucose into all cells esp. hepatocytes by ↑ activity of glucokinase ○ ↑ rate of glycolysis by ↑ activity of phosphofructokinase + glycogen synthetase ○ inhibits glycolysis + glycogenesis</td>
<td>- ↑ rate of K and Mg transport into cells</td>
<td>IM/IV/ subcut/IVI</td>
</tr>
<tr>
<td>Synthetic: recombinant DNA of bovine/human recombinant/porcine insulin</td>
<td></td>
<td></td>
<td>direct effect on LPL Rate of transcriptional and translational events during protein synthesis controls, membrane polarisation + ion transport by activating Na/K/ATPase</td>
<td>- Adipose tissue ○ fat deposition in adipose tissue by ↑ hepatic synthesis of FAs → form TGs ○ activates LPL → splits TGs into FAs → absorbed into adipose tissue and stored ○ inhibits hormone sensitive lipase → prevents hydrolysis of TGs ○ facilitates glucose transport into fat cells → ↑ glycerol → used in manufacturer of storage TGs</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Muscle ○ Active transport of aa into cells ○ ↑ mRNA translation + DNA transcription ○ inhibits catabolism of proteins</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Insulin Brand Information

<table>
<thead>
<tr>
<th>Brands</th>
<th>Onset</th>
<th>Time to peak</th>
<th>Duration</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ultra short acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>insulin aspart (novorapid)</td>
<td>20mins</td>
<td>1hour</td>
<td>4-5hours</td>
<td>Controlling BSL spike post meals</td>
</tr>
<tr>
<td>insulin lispro (Humalog)</td>
<td>30mins</td>
<td>2-3hrs</td>
<td>6-8hr</td>
<td></td>
</tr>
<tr>
<td>insulin glulisine (apidra)</td>
<td>30min-1hr</td>
<td>2-12hr</td>
<td>16-24hrs</td>
<td></td>
</tr>
<tr>
<td><strong>Short acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Actrapid, humulin R, hypurin neutral</td>
<td>1-2hours</td>
<td>4-12hrs</td>
<td>16-24hrs</td>
<td>Intermediate: control BSL between meals</td>
</tr>
<tr>
<td>isophane: humulin NPH, protaphane, hypurin isophan</td>
<td>1-2hours</td>
<td>4-12hrs</td>
<td>16-24hrs</td>
<td></td>
</tr>
<tr>
<td>mixed with short acting insulin (humulin 30-70, mixtard 30/70, mixtard 50/50)</td>
<td>30min-1hr</td>
<td>2-12hr</td>
<td>16-24hrs</td>
<td></td>
</tr>
<tr>
<td><strong>Long acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>isophane: humulin NPH, protaphane, hypurin isophan</td>
<td>1-2hours</td>
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<td></td>
</tr>
<tr>
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<td>30min-1hr</td>
<td>2-12hr</td>
<td>16-24hrs</td>
<td></td>
</tr>
<tr>
<td><strong>Long acting (analogues)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mixed with ultra-short acting (novoMix 30, Humalog Mix 25, Humalog Mix 50)</td>
<td>20mins</td>
<td>1hr</td>
<td>16-18hr</td>
<td></td>
</tr>
<tr>
<td>insulin detemir (leumir)</td>
<td>20mins</td>
<td>1hr</td>
<td>16-18hr</td>
<td></td>
</tr>
<tr>
<td>insulin glargine (lantus)</td>
<td>3-4hrs</td>
<td>9hrs</td>
<td>12-24hr</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1-2hrs</td>
<td>no peak</td>
<td>24hr</td>
<td></td>
</tr>
</tbody>
</table>

**Activity Profiles of Different Types of Insulin**

![Activity Profiles Graph](image)
**Oral hypoglycaemics**

<table>
<thead>
<tr>
<th>Sulfonylureas - gliclazide</th>
<th>Biguanides – metformin</th>
<th>Glitazones / thiazolidinediones - pioglitazone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chem</td>
<td>Biguanide</td>
<td>Glitazones</td>
</tr>
<tr>
<td>Uses 3 generations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pres</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Action</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metab</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toxicity/SE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Route/dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Onset</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Special points</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Sulfonylureas - gliclazide

- **Chem**: S-phenylsulfonylurea structure with substitutions on phenyl ring + urea terminus
- **Pres**: 3 generations
  - 1st generation: tolbutamide
  - 2nd generation: gliclazide, glibenclamide
  - 3rd generation: glimepiride
  All tablet form
- **Action**: Hypoglycaemia → ↑insulin secretion from pancreatic β-cells + may ↑insulin sensitivity
  - binds + inhibits ATP-sensitive K channels on pancreatic β-cells → depolarisation → ↑permeability to K → open voltage gated Ca2+ channels → ↑intracellular [Ca2+] → ↑release of insulin vesicles
- **Uses**: T2DM
- **Pres**: 3 generations
  - 1st generation: tolbutamide
  - 2nd generation: gliclazide, glibenclamide
  - 3rd generation: glimepiride
- **Metab**: ↓TG, cholesterol FFA
- **Toxicity/SE**: Tappedyte, weight gain hypoglycaemia leucopenia/ thrombocytopenia / teratogenic
- **Route/dose**: PO: 40-160mg BD
- **Onset**: Glimepiride: onset 1 hr; max effect 2-4hr
  Tolbutamide: onset 1hr; max effect 5-8hr
- **Duration**: Glimepiride: 24hr
  Tolbutamide: 6-24hr
- **A**: Bioavailability 80-100%
- **D**: 99% bound to albumin
  - VD: gliclazide 0.4L/kg
  - glibenclamide 0.15L/kg
  - glimepiride 0.12L/kg
- **M**: Extensive hepatic metabolism via CYP2C9 to inactive metabolites
- **E**: Renal and GI elimination of active + inactive metabolites
- **Special points**: Crosses placenta → foetal hypoglycaemia CI in renal impairment due to ↑risk lactic acidosis

### Biguanides – metformin

- **Chem**: S-phenylsulfonylurea structure with substitutions on phenyl ring + urea terminus
- **Pres**: All tablet form
- **Action**: Delay glucose absorption + ↑peripheral insulin sensitivity
  - **MoA**: activates AMP activated protein kinase
  - ↑hepatic glucose production
  - ↓glucagon production
  - ↑peripheral insulin sensitivity
  - ↑GLP-1 synthesis in ileum
- **Uses**: T2DM
- **Pres**: 3 generations
  - 1st generation: tolbutamide
  - 2nd generation: gliclazide, glibenclamide
  - 3rd generation: glimepiride
- **Metab**: ↓sensitivity to peripheral actions of insulin by ↓number fo low affinity binding sites for insulin in RBC, adipocytes, hepatocytes, skeletal muscle
- **Other**: Does not cause hypoglycaemia in diabetic pts
- **Toxicity/SE**: Lactic acidosis: ~ inhibition of enzymes involved in aerobic glucose metabolism: ~ anaerobic metabolism → ↑lactate production. Usually lactate quickly converted back to glucose via GNG
- **Route/dose**: PO: 500-2g BD
- **Onset**: Regular release: 2-3hr
  Extended release: 4-8hr
- **Duration**: 24hr
- **A**: Bioavailability 60%
- **D**: Minimally/ nil PB
  - VD: gliclazide 0.4L/kg
  - glibenclamide 0.15L/kg
  - glimepiride 0.12L/kg
- **M**: Not metabolised
- **E**: Renal excreted unchanged in urine
  Clearance ≈ GFR = active secretion
  Elimination ½ life 2-5hrs
- **Special points**: CI in renal impairment due to ↑risk lactic acidosis

### Glitazones / thiazolidinediones - pioglitazone

- **Chem**: S-phenylsulfonylurea structure with substitutions on phenyl ring + urea terminus
- **Pres**: Tablets: 500/850mg metformin hydrochloride
- **Action**: PPARy R inhibition
  - ↓hepatic glucose production
  - ↑hepatic glucose utilisation
  - ↓insulin resistance
- **Uses**: T2DM
- **Pres**: 1st generation: tolbutamide
  - 2nd generation: gliclazide, glibenclamide
  - 3rd generation: glimepiride
- **Metab**: ↓TG, cholesterol FFA
- **Other**: ↓microthrombosis: partial inhibition platelet aggregation + action on vascular endothelium fibrinolytic activity with ↓tissue plasminogen activator activity
- **Toxicity/SE**: Weight gain; fluid retention; hepatic dysfunction
- **Route/dose**: 15-30mg daily
- **Onset**: Regular release: 2-3hr
  Extended release: 4-8hr
- **Duration**: 24hr
- **A**: Bioavailability 60%
- **D**: 99% bound to albumin
  - VD: gliclazide 0.4L/kg
  - glibenclamide 0.15L/kg
  - glimepiride 0.12L/kg
- **M**: Extensive hepatic phase 1 to inactive + active metabolites
- **E**: Renal excreted unchanged in urine
  Clearance ≈ GFR = active secretion
  Elimination ½ life 2-5hrs
- **Special points**: Crosses placenta → foetal hypoglycaemia CI in renal impairment due to ↑risk lactic acidosis

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**METABOLIC AND ENDOCRINE PHYSIOLOGY AND PHARMACOLOGY**

Annelise Kerr
List the main drug groups used in the treatment of diabetes mellitus. For each group explain the mechanism of action and give examples: PAST QUESTION

- DM = metabolic disorder characterised by hyperglycaemia as a result of relative insulin deficiency (i.e. either insulin deficiency or insulin resistance)
- It is associated with macrovascular (CAD, CVD, PVD) and microvascular (diabetic neuropathy, retinopathy, nephropathy) complications

<table>
<thead>
<tr>
<th>Common Types of Hypoglycaemic Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group</strong></td>
</tr>
<tr>
<td>Exogenous insulin&lt;br&gt;(human insulin aspart (NovoRapid) – short&lt;br&gt;insulin glargine (Lantus) – long)</td>
</tr>
<tr>
<td>Sulphonylurea&lt;br&gt;(e.g. gliclazide, glibenclamide)</td>
</tr>
<tr>
<td>Biguanides&lt;br&gt;(e.g. metformin)</td>
</tr>
<tr>
<td>Thiazolidinediones&lt;br&gt;(e.g. rosiglitazone, pioglitazone)</td>
</tr>
<tr>
<td>Alpha-glucosidase inhibitors&lt;br&gt;(e.g. acarbose)</td>
</tr>
<tr>
<td>Dipeptidyl peptidase-4 inhibitor&lt;br&gt;(e.g. sitagliptin, vildagliptin)</td>
</tr>
<tr>
<td>Glucagon-like peptide-1 agonists&lt;br&gt;(e.g. exenatide)</td>
</tr>
<tr>
<td>Meglitinides&lt;br&gt;(e.g. repaglinide)</td>
</tr>
</tbody>
</table>
Corticosteroid drugs

- Uses: adrenocortical deficiency / Allergy / anaphylaxis / Asthma / Autoimmune disorders / Eczema / chemo / immunosuppression post organ tx
- MoA:
  - Control rate of protein synthesis: react with cytoplasmic Rs → form complex that directly influences rate of RNA transcription → directs synthesis of lipocortins
  - Act on HPA axis at receptors on plasma membrane
  - Antiallergic, antitoxic, antishock, antipyretic, immunosuppressive properties
- Effects
  - **Glucocorticoids**
    - **Metabolic:** anti-insulin effect → CHO, protein, lipid metabolism
      - Liver: ↑BSL; ↑gluconeogenesis via aa catabolism; ↑glycogenolysis; ↑KB; ↓peripheral utilisation of glucose
      - Muscle: ↑aa release (↑protein catabolism); ↓glucose ptake; ↑FFA metabolism
      - Adipose tissue: ↑lipolysis / ↑FFA release; ↓fat storage
      - Overall: ↑plasma glucose, lipid, ketone levels
    - **Anti-inflammatory:** immunosuppressive; ↓mast cell degranulation; ↓capillary permeability; ↓effects lymphokines
    - **CNS:** excitatory
    - **CVS:** ↓contractility, vasoconstriction by ↑number + stimulating action of α1 + β-adrenoceptors
    - **Bone:** ↓bone formation / ↓collagen synthesis / ↑OC activity → OP
    - **Haem:** ↑RBC / ↑platelets; ↓WCC/eosinophils
    - **GIT:** ↓PG synthesis → ↓stress ulceration
    - **Permissive effect:** required for glucagon + catecholamines to exert effect
    - **NB glucocorticoids antagonise effects of anticholinesterase drugs**
  - **mineralocorticoid:**
    - Na retention+++; ↑K excretion; ↑urinary Ca2+ excretion
    - NB In large dose: inhibits endogenous adrenal cortical secretion, thymic activity, and ACTH excretion
    - Aldosterone:
      - ↑Na/C/H2O reabsorption in DCT + CD via:
        - upregulate + activate basolateral Na-KATPase → via MR in principal cells → conc gradient for Na+ reabsorption
        - upregulates apical ENaC → ↑permeability to Na+ → ↑reabsorption
        - stimulation of Na/H pump in intercalated cells DCT
      - ↑K excretion
    - Mineralocorticoid SE: Na+ + water retention / ↓K / Oedema / muscle weakness/ steroid myopathy / HTN / PUD, pancreatitis, oesophagitis
**Hydrocortisone**

- Synthetic glucocorticoid
- Vials: white lyophilized powder diluted in water → 100mg of hydrocortisone sodium succinate
- Topical creams

**Prednisolone**

- Synthetic glucocorticoid
- Tablets: 1 / 2.5 / 5 / 20mg
- Solution for injection 25mg/ml prednisolone acetate drops

**Methylprednisolone**

- Synthetic glucocorticosteroid
- Tablets: 2/4/8/16/32
- Injectable suspension 20/40/80mg/ml
  - Powder for injection: 40/125/500/1g/2g

**Dexamethasone**

- Synthetic glucocorticosteroid
- Tablets 0.5/2mg/oral solution
  - IV dexamethasone sodium phosphate 3.8mg/ml
  - Topical creams

**Fludrocortisone**

- Synthetic mineralocorticoid
- Tablets: 0.01/0.02mg
- Oral solution 50/100microg daily

**Relative DE**

- Hydrocortisone: 100mg
- Prednisolone: 25mg
- Methylprednisolone: 20mg
- Dexamethasone: 4mg

**Route/ dose**

- Hydrocortisone: IV: 100-500mg 6-8hrly
  - PO: 10-20mg/day
- Prednisolone: PO: 5-60mg/day
  - IV: 10-20mg/day
- Methylprednisolone: PO/ IV/ IM
  - PO 1-9mg
  - IV
- Dexamethasone: PO 1-9mg
  - IV: 50-100microg daily

**Onset**

- Hydrocortisone: IV: 5min / PO: 1hr
- Prednisolone: PO: 1-2hr
- Methylprednisolone: PO <5min
- Dexamethasone: IV <1.5hr

**Duration**

- Hydrocortisone: 8hrs
- Prednisolone: 18-36hr
- Methylprednisolone: PO:36hrs
  - IM: 1-4weeks
- Dexamethasone: PO 1-9mg
  - IV: 50-100microg daily

**A**

- PO: bioavailability 50%
- PO: bioavailability 80-100%
- Vd 0.3-0.5L/kg according to dose
- 70% protein bound; high uptake in liver, kidney, adrenals
- Bioavailability 100%

**D**

- Variable PB depending on conc
  - Reversibly bound to albumin (20%) + specific corticosteroid binding globulin (70%)
  - Low conc: 90% PB
  - High conc: 60% PB
  - Vd 0.3-0.5L/kg according to dose
- Reversibly bound to albumin (20%) and specific corticosteroid binding globulin (70%)
  - Low conc: 90% protein bound
  - High conc: 60% protein bound
  - Vd 0.3-0.7L/kg according to dose
- Vd 1L/kg

**M**

- Liver
  - To tetrahydrocortisone
- Liver
  - Hydroxylation → conjugation
- Liver

**E**

- Clearance dose dependent: 150-250ml/min
  - Elimination ½ life 2hrs
- Clearance dose dependent: 170-200ml/min
  - Elimination ½ life 2-5hrs
- Urine
  - Elimination ½ life 3hr
  - Total body clearance 16L/hr
- Glucocorticoids antagonize effects of anticholinesterase drugs
  - 1.2 life 4hr

**Special points**

- Hydrocortisone = Prednisolone = Methylprednisolone
- ¼ as potent as prednisolone
- Prednisone/ prednisolone = interchangeable (latter active)
- Conversion of prednisone to prednisolone rapid + extensive - occurs as 1st pass effect in liver
  - 4x more potent than hydrocort
  - 6x less potent than dex
- PO 1-9mg

**Relative mineralocorticoid effect**

- +++
- ++
- +

---

**Describe the therapeutic and unwanted effects of dexamethasone:** PAST QUESTION

General: dexamethasone = synthetic glucocorticoid
- nil mineralocorticoid activity
- 25-30x potency of hydrocortisone
- produce effect by activation of intracellular steroid receptors → modification of gene transcription within nucleus of cell
- therapeutic effects
  - PONV prophylaxis: MoA unknown; 4-8mg 1-2hrs prior to end of anaesthesia → 24hrs 4risk PONV; requires single dose only
  - Anti-inflammatory/ immunsuppressive:
    - Prevent inflammatory response
    - ↓vascular permeability/ proliferation, ↓edema
    - ↓inflammatory cell activity (leukocytes, mononuclear cells)
    - ↓hypersensitivity response after antigen-antibody reactions
    - ↓immune mediators (cytokine production, PAF, complement components)
- Regulatory action
HPA axis
- -ve feedback suppression of endogenous corticosteroid production
- useful for suppression of ACTH production
- treatment in addisons disease

Unwanted effects
- ↓wound healing/ ↑risk infection/ ↑risk thrush/ breakdown bowel anastomoses
- suppression of endogenous corticosteroid production: requires tapering dose to avoid Addisonian crisis
- metabolic action
  - CHO: ↑gluconeogenesis, glycogenesis, ↑BSL, ↓cell uptake glucose
  - Proteins: ↑catabolism, ↓anabolism
  - Fats (after prolonged use): ↑lipolysis, redistribution of fat (cushings)
- Other
  - OP
  - ↑IOP, glaucoma
  - peptic ulceration
  - mental disturbance
  - Na/H2O retention
<table>
<thead>
<tr>
<th>Thyroxine</th>
<th>Propylthiouracil</th>
<th>Carbimazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chem</td>
<td>Iodine containing amino acid derivatives of thyronine</td>
<td>Hyperthyroidism: graves disease</td>
</tr>
<tr>
<td>Uses</td>
<td>Hypothyroidism</td>
<td>Thyrotoxic crisis</td>
</tr>
<tr>
<td>Pres</td>
<td>Tablets: 25/50/100microg levothyroxine sodium</td>
<td></td>
</tr>
<tr>
<td>Action</td>
<td>Modulation of growth + metabolism</td>
<td>Inhibits synthesis of thyroid hormone by blocking oxidation of iodine in thyroid gland</td>
</tr>
<tr>
<td>MoA</td>
<td>MoA: thyroid hormones combine with receptor protein within cell nucleus → activate DNA transcription → ↑rate RNA synthesis + ↑protein synthesis</td>
<td>Anifthyroid action due to conversion to methimazole</td>
</tr>
<tr>
<td>CNS</td>
<td>↑excitability, seizures, tremor</td>
<td></td>
</tr>
<tr>
<td>CVS</td>
<td>↑HR, ↑tachycardia, ↑TCO, ↓SVR, ↓DBP</td>
<td></td>
</tr>
<tr>
<td>Resp</td>
<td>↑MV due to ↑CO2 production</td>
<td></td>
</tr>
<tr>
<td>MSK</td>
<td>↑OB activity</td>
<td></td>
</tr>
<tr>
<td>Metab</td>
<td>↑BMI up to 100%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>↑CHO metabolism (↑glucose uptake, ↑glycolysis, ↑glucoseogenesis)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>↑fat metabolism (↑lipolysis, ↑non shivering thermogenesis, ↓plasma cholesterol, ↓plasma phospholipids, ↓TGs)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>↑protein metabolism (↑anabolism at physiological levels, ↑catabolism at high levels)</td>
<td></td>
</tr>
<tr>
<td>Toxicity/SE</td>
<td>Thyrotoxicosis</td>
<td>Hepatitis</td>
</tr>
<tr>
<td>Route/ dose</td>
<td>PO: 25-300microg daily divided doses titrated to response</td>
<td>PO: 50-150mg q8hr up to 300mg 4-6hr in crisis</td>
</tr>
<tr>
<td>Onset</td>
<td>24hr to onset; peak effect in 6-7days</td>
<td>Peak effect 1-2hr</td>
</tr>
<tr>
<td>Duration</td>
<td>12-24hr</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>100% absorption</td>
<td>80% PB</td>
</tr>
<tr>
<td>D</td>
<td>Bound to thyroid binding globulin and thyroid binding pre albumin in plasma &gt;99%</td>
<td>VD 0.4L/kg</td>
</tr>
<tr>
<td></td>
<td>VD levothyroxine 0.2L/kg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>VDT3 0.5L/kg</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>33% levothyroxine converted to triidothyronine in periphery (liver and kidney) + rT3 → conjugation to glucuronide + sulfate</td>
<td>Liver to glucuronide conjugates, inorganic sulfates, sulfur metabolites</td>
</tr>
<tr>
<td>E</td>
<td>20-40% in faeces unchanged</td>
<td>Urine 35%</td>
</tr>
<tr>
<td></td>
<td>clearance of levothyroxine 1.7ml/kg/min; elimination ½ life 6-7days</td>
<td>Elimination ½ life 102hr</td>
</tr>
<tr>
<td></td>
<td>clearance of T3: 17ml/min; elimination ½ life 2 days</td>
<td>Clearance 7L/hr</td>
</tr>
<tr>
<td>Special points</td>
<td>Anticoagulant activity of warfarin B blockers interfere with the conversion of levothyroxine to T3 → inactive rT3</td>
<td></td>
</tr>
</tbody>
</table>
### Glucagon, Vasopressin and analogues

<table>
<thead>
<tr>
<th>Glucagon</th>
<th>Vasopressin (ADH)</th>
<th>terlipressin</th>
<th>Desmopressin (DDAVP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chem</td>
<td>Polypeptide hormone extracted from islets of langerhans</td>
<td>Synthetic nonapeptide analogue of endogenous arginine vasopressin (ADH)</td>
<td>Vasopressin analogue</td>
</tr>
<tr>
<td>Uses</td>
<td>Hypoglycaemia</td>
<td>Diabetes insipidus</td>
<td>Bleeding oesophageal varices</td>
</tr>
<tr>
<td></td>
<td>Radiological investigation of GIT</td>
<td>Uncontrolled haemorrhage with oesophageal varices</td>
<td>Hepatorenal syndrome type 1 in pts considered for transplant</td>
</tr>
<tr>
<td></td>
<td>Cardiogenic shock</td>
<td>Catecholamine refractory septic shock</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Propranolol overdose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pres</td>
<td>Vials 1/10mg lyophilized glucagon hydrochloride with lactose reconstituted in glucose + water prior to use</td>
<td>Terlipressin: CCS</td>
<td>CCS</td>
</tr>
<tr>
<td></td>
<td>Prefilled syringes 1mg glucagon</td>
<td>Desmopressin: oral lyophilizate</td>
<td>White powder</td>
</tr>
<tr>
<td>Action</td>
<td>Acts via cell membrane receptors which stimulate AC activity</td>
<td>Vasoconstriction</td>
<td>V2&gt;V1</td>
</tr>
<tr>
<td></td>
<td>Final effects mediated via cascade of protein kinases</td>
<td>V1 Rs: vascular smooth muscle/platelets: Gq proteins</td>
<td>V2 agonist</td>
</tr>
<tr>
<td></td>
<td></td>
<td>V2 Rs: CD; Gs proteins</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>V3 Rs: ant pit</td>
<td></td>
</tr>
<tr>
<td>CVS</td>
<td>+ve inotrope</td>
<td>Vasoconstriction via V1 Rs on vascular smooth muscle in splanchnic + portal circulation</td>
<td>Vasoconstriction</td>
</tr>
<tr>
<td>AS</td>
<td>4x in GIT</td>
<td>Vasoconstriction</td>
<td>Lacks vasoconstrictor effects due to minimal V1 agonism</td>
</tr>
<tr>
<td>Metab</td>
<td>1-glucocorticoid/glycogenolysis / +BSL</td>
<td>Vasoconstriction</td>
<td>Haemostatic agent</td>
</tr>
<tr>
<td></td>
<td>Tipolysis / +etokinesis</td>
<td></td>
<td>Platelet dysfunction: ?xWF</td>
</tr>
<tr>
<td></td>
<td>+proteolysis</td>
<td></td>
<td>+platelet adhesion</td>
</tr>
<tr>
<td>Other</td>
<td>small T/UO + RFB</td>
<td>+vWF; Tuterine contraction</td>
<td>Antidiuretic: act on renal CT to +permeability to water reabsorption</td>
</tr>
<tr>
<td>Tox/ SE</td>
<td>Hypokalaemia (2o + insulin secretion); N+V+D</td>
<td>Headache/bradycardia/hypokalaemia/ ↓Mg/ ↓TQT</td>
<td>Effect of FVIII: FVIII coagulant activity + vWF</td>
</tr>
<tr>
<td>Route/ dose</td>
<td>IV/ IM/ SC 1-5mg</td>
<td>PO/ intranasal / IV</td>
<td>Rare: tachycardia, flushing, headache</td>
</tr>
<tr>
<td></td>
<td>IV: 1-20mg/hr</td>
<td>PO: intranasal / IV</td>
<td>Hyponatramia (2: diuretic effect)</td>
</tr>
<tr>
<td>Onset</td>
<td>IV: &lt;1 min; SC 8min</td>
<td>PO/ intranasal / IV</td>
<td>Rare: arterial thrombotic events</td>
</tr>
<tr>
<td>Duration</td>
<td>TBSL lasts 10-30mins</td>
<td>PO/ intranasal / IV</td>
<td>Recycled into aa pool</td>
</tr>
<tr>
<td>A</td>
<td>Inactive when PO</td>
<td>PO/ intranasal / IV</td>
<td>Elimination 1% unchanged in urine</td>
</tr>
<tr>
<td>D</td>
<td>Not protein bound</td>
<td>PO/ intranasal / IV</td>
<td>Similar to ADH; nil info on PB</td>
</tr>
<tr>
<td>M</td>
<td>Degraded by proteolysis by splanchnic, hepatic, renal routes</td>
<td>Vasopressinases (peptidases to amino acids)</td>
<td>Peptidases</td>
</tr>
<tr>
<td>E</td>
<td>Clearance 8-12ml/kg/min</td>
<td></td>
<td>Peptidases</td>
</tr>
<tr>
<td></td>
<td>Elimination ½ life 3-6mins</td>
<td></td>
<td>Peptidases</td>
</tr>
<tr>
<td>Special points</td>
<td>Clearance ½ in pts with renal failure</td>
<td></td>
<td>Peptidases</td>
</tr>
<tr>
<td></td>
<td>Not removed by haemodialysis</td>
<td></td>
<td>Peptidases</td>
</tr>
<tr>
<td></td>
<td>Potentiates anticoagulant effect of warfarin</td>
<td></td>
<td>Peptidases</td>
</tr>
</tbody>
</table>

**Chem:** α cells of pancreatic islets of langerhans

**Action:** Acts via cell membrane receptors which stimulate AC activity → ↑[cAMP]

**Antidiuresis + vasoconstriction**

**V1 Rs:** vascular smooth muscle/platelets: Gq proteins → IP3/DAG → Ca2+ → vasoconstriction + platelet aggregation

**V2 Rs:** CD; Gs proteins → cAMP → Ca2+ → insertion of aquaporins

**V3 Rs:** ant pit → ACTH release

**Vasoconstriction:**

- Acts as a prodrug → converted via enzymatic cleavage of 3 glygyl residues to biologically active lysine vasopressin

- V2>V1

- V2 agonist

- Intracellular [cAMP]

- Exocytosis vWF + FVIII + tissue plasminogen activation

**Antidiuretic:**

- Water permeability in renal tubular cells

**CVS:** +ve inotrope +ve chronotrope +ve inotrope relaxation of smooth muscle

**AS:** +ve in GIT inhibit pancreatic + gastric secretions ↓ureteric tone

**Metab:** 1-glucocorticoid/glycogenolysis / +BSL

**Other:** small T/UO + RFB

**Tox/ SE:** Hypokalaemia (2o + insulin secretion); N+V+D ↓cutaneous + splanchnic perfusion

**Route/ dose:** IV/ IM/ SC 1-5mg

**Onset:** IV: <1 min; SC 8min

**Duration:** TBSL lasts 10-30mins

**A:** Inactive when PO

**D:** Not protein bound Vd 0.14L/kg

**M:** Degraded by proteolysis by splanchnic, hepatic, renal

**E:** Clearance 8-12ml/kg/min

**Special points:** Clearance ½ in pts with renal failure

**Potentiates anticoagulant effect of warfarin**