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

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** (O_2, N_2, CO_2, EtOH)
        - Small, highly soluble lipid molecules dissolve directly in lipid bilayer + diffusion through CM via conc gradient

     ii. **Simple diffusion – lipid insoluble** (H_2O)
        - 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; Δshape in response to electrival stimulus (e.g. AP)
          - Chemical/ ligand: e.g. ACh, GABA, glycine, NMDA; binding of ligand → open / close

     iv. Facilitated diffusion
        - E.g. glucose, amino acids
        - Via carrier protein: binds substrate → conformational change → 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

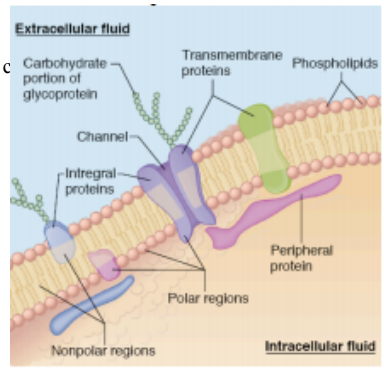
     ii. Secondary active transport
        - Combination of primary active transport + facilitated diffusion
        - Dependent on energy potential formed by EC gradient set up by primary active transport
        - Classified as:
          - Co transport / symport: both ions move in same direction e.g. SGLT-2
          - Counter transport: ions in opposite directions e.g. Na/K antiporter in CD
   - Factors affecting active transport
     - Concentration difference across CM
     - Electrical portential difference
     - 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 → 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 cells 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; c 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 mitochrondria. Outline the metabolic processes that occur in the mitochrondria: 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 → molecules <5kDa diffuse across
- 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 va 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 mitochrondria
  - 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

Composition

- intracellular fluid vol = ~23L; 55% of 42L ot TBW in 70kg adult male
- High protein, K and Mg; low Na and Cl

	Substance	Extracellular	Intracellular
E	Na+	140 mmol/L	10 mmol/L
I	K+	4 mmol/L	140 mmol/L
E	Ca2+ (free)	2.5 mmol/L	0.1 micromol/L
I	Mg2+	1.5 mmol/L	30 mmol/L
E	Cl-	100 mmol/L	4 mmol/L
E	HCO3-	27 mmol/L	10 mmol/L
I	PO4	2 mmol/L	60 mmol/L
E	Glucose	5.5 mmol/L	0-1 mmol/L
I	Protein	2g/dL	16g/dL

Control of intracellular fluid

- 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 conc non-diffusible ions (proteins/ organic phosphates that cannot cross the CM
    - Interstitial fluid has ↓[protein]
    - NB at equilibrium, electroneutrality would be preserved there is ↑osmolality intracellularly (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 extracelluar Na balances the Gibbs-Donnan effect due to impermeant intracellular colloids → double-Donnan effect stabilises cell volume

What happens when cells are stressed by a change in ECF tonicity?

- Acute ΔECF tonicity → acute Δcell volume
  - Water crosses CM freely → Δtonicity can have rapid effects on cell vol.
  - Hypertonic ECF → causes cells to shrink: cells ↓ 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 ↓s towards normal due to volume regulatory decrease → due to loss of intracellular solute esp. K+
- Slow change in tonicity
  - Cells adapt as tonicity is slowly changed - loss or gain solute at a rate which almost matches the effect o change in tonicity
- E.g. chronic vs. acte hyponatraemia

Generation of the trans-membrane potential

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

Neural tissue (Neurons):

- 2 characteristic structural + functional features: excitable membrane, + synapses
- Excitability = ability of neurons to generate + propagate electrical impulses (AP)
- 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

Key equation: the Nernst equation

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

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

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
     - Osmotic effect: ↑ECF [Na+] balances osmotic effect of ↑intracellular conc of –vely charged protein
     - Electrogenic effect: cell interior hyperpolarised
3. **Gibbs Donnan effect**
   - Minor contribution to RMP
   - unequal distribution of large –vely charged protein, impermeable to CM → affects distribution of other diffusible ions (K, Cl) and hence RMP by ~-10mV

Principles

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

Key equation: the Goldman–Hodgkin–Katz equation

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

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

Note:

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

Typical RMPs of various cells

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

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) → Δtransmembrane voltage -_> threshold → channel opens → 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 doen 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
  - Selective
  - 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) → ionise in cytosol and binds to H gate preventing it from leaving inactive state
- nAChR:
  - mostly post synaptic ligant gated cation channel found in NMJ
  - 5 subunit R with central cation pore
  - ACh binds to 2α subunits → conformational change in R → opening of cation pore → influx Na+ / efflux K → 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: heterotrimetric 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 ion channels
  - **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. Gai triggers breakdown of cGMP
- Targets: G protein can activate (2nd messengers)
  - Adenylate 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

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

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 2α 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 1° brown fat

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
    i. 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

    ii. 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

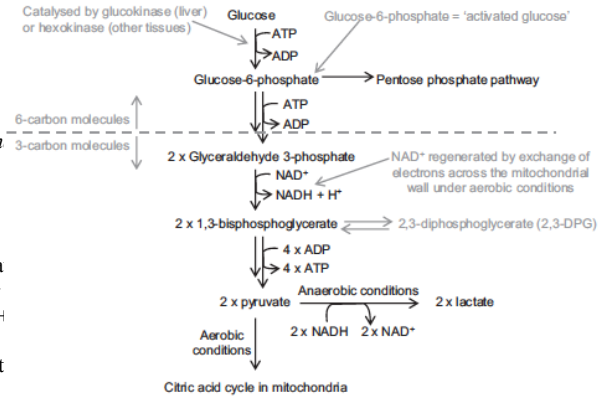
Carbohydrate metabolism:

- glucose = basic unit of carbohydrates
- Active form of glucose = glucose-6-phosphate

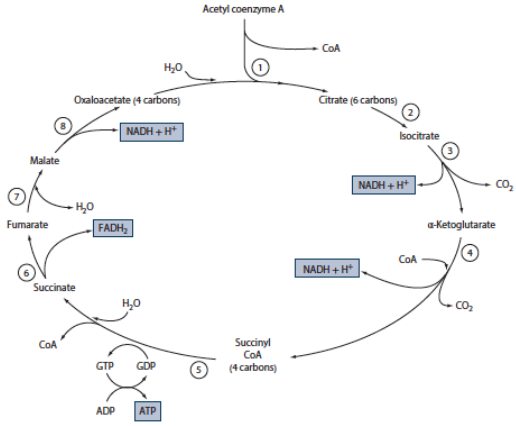
Carbohydrate catabolism:

Carbohydrates (glucose) can be metabolised by 3 pathways

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



2. Hexose monophosphate shunt/ pentose phosphate pathway
   - Produces pentose sugars for nucleic acid synthesis + NADPH for intracellular reduct
   - 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 + FADH
   - 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+ → ac
     - B-oxidation of FAs (from fat metabolism)
     - NB keto-acids (from protein metabolism) can also enter TCA
   - 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+ + FAD + ADP + Pi + 2H2O → CoA-SH + 3NADH + FADH2 + 3H+ + ATP + 2CO2



Overall one molecule of glucose yields:

- anaerobic metabolism = 2ATP (glycolysis only)
- aerobic metabolism = 36 ATP (glycolysis + TCA + ETC)

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

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 + FFAs
  - **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 → FFAs + glycerol → diffuse into fat (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

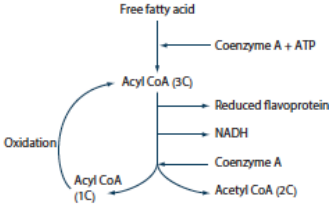


Figure 12.6 β-oxidation of free fatty acids.

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

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

- Ketone bodies:
  - Excess acetylCoA 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 βcells of pancreas in response to ↑BSL
- structure: 2 chains (A chain + B chain) linked by disulphide bridge
- secreted when extracellular Ca2+ enters the βcells 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 acetylCoA (*pyruvate dehydrogenase – activated by insulin)* → synthesised into FFAs (*acetyl-CoA carboxylase – 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 → FFAs + glycerol → taken up by fat cells + reconverted back and stored as TGs
    - stimulates GLUT4: ↑glucose uptake in fat cells → form glycerol to further esterify FFAs 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
    - iii. Occurs in liver
    - iv. Catalysed by deaminase enzymes
    - v. Amino group removed → produces keto acid + NH3
  - 2. Transamination
    - vi. amino group transferred (through catalysis by aminotransferases) to a keto acid or other amino acid → to form new amino acid
    - vii. 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

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

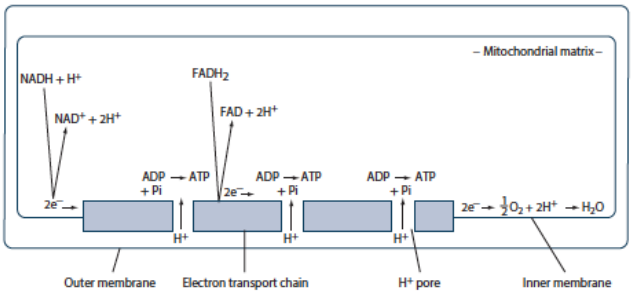


Figure 12.5 Diagrammatic representation of a mitochondrion, showing the proteins forming the electron transport chain on the inside surface of the inner mitochondrial membrane.

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)
  - Glycogenolysis
    - xii. When plasma glucose levels ↓ → release of glucagon + adrenaline stimulates 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: 3.5-5.5mmol/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, ↑esterification of FAs (to make TGs) in adipose tissue
  - 3. Inhibition of endogenous glucose production: insulin inhibits lipolysis + glycogenolysis + gluconeogenesis
  - 4. Cellular uptake of amino acids and K
    - xiii. ↑amino acid uptake → promoes 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

- secretion:
  - stimulated by hypoglycaemia: hypoglycaemia-induced ↑ANS activity (i.e. indirect) + ↑adrenaline
  - inhibited by: insulin, somatostatin, ↑freeFA and ketone body concentrations
- Actions:
  - ↑plasma glucose concentration by:
    - xv. promoting gluconeogenesis
    - xvi. promoting glycogenolysis
    - xvii. inhibiting glycolysis in liver
  - Esp. important during starvation

Anaerobic metabolism

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

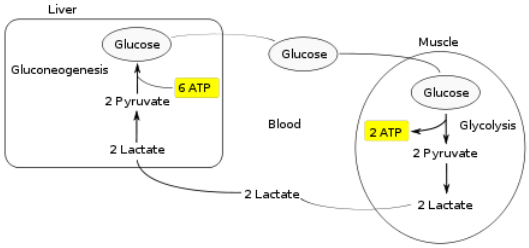
- Aerobic conditions: pyruvate passes into mitochrondrion → enters *citric acid cycle*
- Anaerobic conditions: TCA cannot operate → ETC is dependent upon O2 and is needed to regenerate NAD+ and FAD for use in TCA
- lactate = 3C organic acid produced as a result of anaerobic metabolism of pyruvate catalysed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

- ~~Beta oxidation of FAs → major source of energy~~
- if CHO are scarce (starvation) or unable to enter cell (DKA) → fat metabolism = main source of energy
- Liver: β-oxidation of FFA → ↑mitochondrial acetyl-CoA → condensation of 2 acetyl-CoA → acetoacetate, beta-hydroxybutyrate, acetone = ketone bodies
- ↑ketone bodies 2o imbalance between flow of FAs into mitochrondria of hepatocytes and capacity of TCA to remove acetyl CoA
- Ketone bodies released from hepatocytes → utilised in tissues
    - Muscle: converts KBs back into acetyl-CoA → enters TCA
    - heart: can use KBs as energy during starvation
    - brain: usually glucose dependent; in starvation can adapt to using KBs
    - NB: RBCs do not have mitochrondria, so are entirely dependent on glycolysis for their metbaolisma nd are unable to utilise KBs
- Glucagon + epinephrine stimulate lipolysis and ↑ketone production

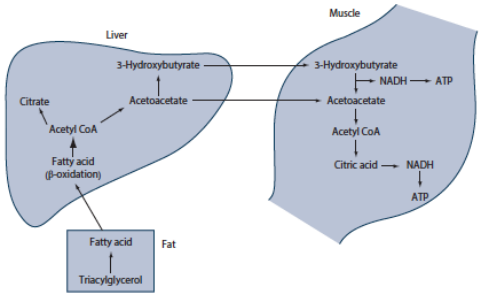


Figure 12.15 Ketone acid synthesis.

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 hydrolyes 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 itilising ATP derived from oxidative phosphorylation
    - muscle contraction lasting secs – 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 mitochrondria to form ATP
        - Muscle glycogen + blood glucose = 50% energy release in active muscle
        - FAs important for prolonged exercise
        - B-oxidation of FAs within mitochrondria → acetyl CoA → TCA → ATP

Describe the physiological consequences of starvation

Starvation

- 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 mitochrondria → 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 nutition 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: wernickes 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 cardioresp system stressed by starvation
    - Excessive Na + water retention → may precipitate LVF

- Reintroduction of CHO → ↑resp quotient
- Mx: slow institution of feeding + aggressive correction of electrolytes; vitamin supplements

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%

General:

- Fluid requirements 30ml/kg/day; minimal energy requirement 30kcal/kg/day
- Fasting = period of no food or fluid intake
  - early fasting = <24hr; sustained fasting = >24hr
  - 6hr fast = normal physiological event daily; well tolerated
  - 20hr fast = requires significant mobilisation of reserves
  - Sustained fasting → many organs alter substrate utilisation pattern to preserve glucose for brain
  - Liver = central in adaptive process whereby BSL is maintained by the conversion of fat + amino acids to glucose
- Starvation = state of relative or absolute inadequate energy supply

Glucose

- Primary energy source for brain + neural tissue (obligatory glucose utilisers), + main fuel for RBC, kidney
- BSL must be tightly maintained (3.5-6mmol/L)
- Glucose stored in circulation (5g) + ECF (10g) → ~2hr supply
- Glucose stored as glycogen in liver (~100g) + muscle (400g) → 12-24hr supply

Phase	Details	Hormonal Δ	BSL maintained by:

6hr fast = **glycogenolytic phase**	Counteract ↓BSL by breakdown of glycogen stores	↓insulin
		↑adrenaline
		↑ADH
			Liver:
			- ↑glycogenolysis + ↓glycogen synthesis
			- ↑gluconeogenesis (minor). Substrates obtained from:
			  ○ 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 (↓glycogen synthesis)
			- ↓glucose uptake (via ↓insulin dependent LUT4)
			- ↓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**	Counteract further ↓BSL by mobilising substrates for gluconeogenesis in liver	↓insulin
		↑glucagon (peak d4)
		↑adrenaline
		↑cortisol
		↑GH (48h)
			Liver:
			- Glycogen stores depleted/ exhausted
			- ↑↑gluconeogenesis.
			  ○ Cori cycle: lactate + pyruvate
			  ○ Muscle: ↑protolysis → alanine + aa's
			  ○ Adipose tissue: ↑glycerol
			Muscle: ↑protein catabolism / ↑aa release / ↓protein synthesis / ↓glucose uptake
			Adipose tissue: Lipolysis → ↑FFA / ↑glycerol release
			Water: ↑osmolality ↓blood vol → osmoreceptors → ↑thirst, ADH, SY, RAAS

Sustained fasting >96hr **Ketogenic phase**	Energy supply mainly from fat → ketone bodies	↓insulin
		↑glucagon
		↑cortisol
		↑adrenaline
		↓T3
			Aim: glucose conserved; body uses fat + spares protein; brain + nerves adapt to use ketone bodies; ↓BMR
			Liver: ↓gluconeogenesis
			Adipose tissue: ↑ketogenesis
			- Lipolysis → ↑FFA + ↑glycerol
			  ○ FFA provides energy for gluconeogenesis
			  ○ Glycerol synthesised into glucose by liver + kidney
			- Ketogenesis
			  ○ Oxidation of FFA to acetoacetate + βhydroxybutyrate (ketone bodies)
			  ○ Ketone bodies: transfer of CoA from succinylCoA to acetoacetate to return back acetylCoA to enter TCA

NB: Lipolysis: TG broken down by HSL → ↑FFA / ↑glycerol release → converted to acetylCoA via βoxidation to enter TCA

Hormones involved in regulation of BSL: MAKEUP

Response to ↓BSL

Homrone	stimulus	Response		
		Liver	Muscle	Adipose tissue
↓Insulin	↓BSL detected by βcells of IoL	↑glycogenolysis ↑gluconeogenesis ↑KB (small) ↑glucose release ↓glycogenesis	↑glycogenolysis ↓glycogenesis ↓glucose uptake (↓GLUT4) ↓protein synthesis	↓glucose uptake (↓GLUT4 transporter insertion) ↓fat uptake (↓LPL) ↑FFA release
↑adrenaline	Stimulated by ↓BSL, stress	↓glycogenesis ↑glucose release ↑KB pancreas: inhibit insulin	↓glucose uptake ↑FFA metabolism	↑FFA release ↓glucose uptake
↑Cortisol ↑GH	Stimulated by ↓BSL, stress	↑gluconeogenesis ↑glucose reelase	↓protein synthesis ↑aa release	↑FFA release

		↑KB	↑FFA metabolism	
↑glucagon	↓BSL detected by αcells of IoL peak release day 4	↑gluconeogenesis ↑aa catabolism ↑KB	Minimal effect	Minimal effect

Discuss the factors that influence metabolic rate

Background

- Metabolism
  - biochemical rxns that occur within living organisms → energy required to sustain life. Involves: anabolism + catbolism
  - 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:
    - mental and physical rest
    - environmental temperature
    - fasted for 12 hours
  - in healthy adult = ~70-100kcal/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
  - When environmental temp critically low → ↓enzyme activity → ↓MR
  - ↑environmental temp → ↑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 (VO2) + 1.1 (VCO2)] 1.44 (KCal/Day)
- 3 main methods used in indirect calorimetry:
  - 1. Benedict-Roth spirometer: 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 ↓s 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 pocess

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 electolytes/ 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. glucoagon balance (act on liver, muscle, adipocytes)
  - Renal (excretion)
  - Modulated by: catecholamines, cortisol, thyroid homrones
    - short term regulation: via secretion or inhibition of insulin + glucagon from pancreatic islets
    - long 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
- **Pancreatic alpha cells** → sense ↓BSL
  - ↑glucagon release

Effectors

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

- ↑GLUT4 insertion into cell membrane → ↑glucose uptake into cells esp. muscle + fat
- ↑glycogen synthesis
- ↑glucose utilisation + ↑fat and protein synthesis
- ↓glycogenolysis / ↓gluconeogenesis

- **glucagon**: secreted in reponse to ↓BSL → following effects to ↑BSL
  - ↑glycogenolysis / ↑gluconeogenesis
  - minimal effect on adipose tissue and muscle
- **Adrenaline**: stimulated by ↓BSL, stress
  - Inhibit insulin
  - Liver: ↓glycogenesis, ↑glucose release, ↑KB
  - Fat: ↑FFA release, ↓glucose uptake
  - Muslce: ↓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

BSL (mmol.L^{-1})	Symptoms	Endocrine Response
4.6		Insulin secretion inhibited
3.8	Autonomic dysfunction	Glucagon, adrenaline, and GH secretion
2.8	CNS dysfunction	
2.2	Lethargy, Coma	
1.7	Convulsions	
0.6	Permanent brain damage, Death	

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

BSL normally maintained 4-7mmol/L
- maintained by –ve feeback system
  - detector: islets of Langerhans cells in pancreas
  - stimulus= BSL
  - effector = insulin:glucagon release ratio
  - aim: maintain BSL to provide substrate for obligate glucose metbaolisers (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, ↑SVR, 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 (↑intracelular hormone sensitive lipase)
  - muscle
    - ↓glucose uptake (↓GLUT4)
    - ↓protein synthesis
    - ↓glucogenesis
    - ↑FFA metabolism
  - liver
    - ↑glucose release (glycogenolysis)
    - ↑FFA release (some ketone body formation)
    - ↑gluconeogenesis via glycerol (fats) and lactate (RBC metabolism)
- **↑catabolic homrones:** ↓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 → ↓BP + ↓HR
  - Post hypothalamic stimulation → ↑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 neurosecreotry neurons
  - Magnocellular neurons: consists of SON + PVN; synthesise and secrete ADH and oxytocin
  - Parvocellular neurons: form tuberoinfundibular tract → secrete hypophysiotropic hormones; release controlled by Nad, dopamine, 5-HT
- Hypothalamic hormones → action in pituitary
  - Anterior pituitary by hormone secretion into long portal vein
    - GnRH → stimulates FSH + LH release
    - CRH → stimulates ACTH release
    - GHRH → stimulates GH release
    - TRH → stimulates TSH release
    - Somatostatin (GH inhibiting hormone) → inhibits GH, TSH, ACTH, and PRL release
    - PRL releasing hormone (PRH): stimulates PRL release
    - Dopamine → 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

Pituitary

- 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

Location	Hormone	Action	Stimulated by:	Inhibited by:
Anterior pituitary	ACTH	Short chain peptide Stimulates cortisol release from zona fasiculata	CRH	Cortisol
	TSH	Glycoprotein Stimulates synthesis + release of T3 + T4	TRH	T3
	FSH	Glycoprotein gonadotropin Females: stimulates oestrogen synthesis + ovarian follicle development Males: stimulates sperm maturation	GnRH	Sex steroids
	LH	Glycoprotein gonadotropin Females: rapid ↑stimulates ovulation + corpus luteum development Males: stimulates testosterone synthesis		
	GH	Long chain peptide released in pulsatile fashion Anabolic effects: directly stimulates lipolysis → ↑FFA Indirectly stimulates IGF-1 release → promoting cell growth + development	GHRH High with exercise, hypoglycaemia, stress	Somatostatin IGF-1
	Prolactin	Long chain peptide breast development during gestation + lactation post delivery		
Posterior pituitary	ADH	Short chain peptide Acts on: - V1 R in vascular smooth muscle → vasoconstriction - V2 R in CD (↑water reabsorption) + endothelium (↑vWF + FVIII release) - V3 R in pituitary → timulate ACTH release	Hypothalamic neural stimulus	
	Oxytocin	Short chain peptide; structurally similar to ADH Causes: uterine contraction, let down reflex, psychological, bonding		

Thyroid hormones

Describe the physiological actions of thyroid homrones: 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 aa 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

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

Thyroid hormone synthesis: MAKEUP

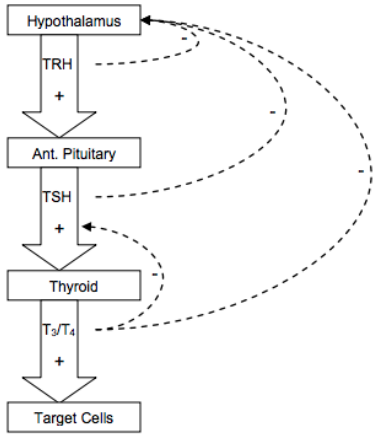
Synthesis

- 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 then di-iodotyrosine (*peroxidase*)
  - di-iodotyrosine + di-iodotyrosine = thyroxine (T4) (*perixodase)* → 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 homrones

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

Negative feedback



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Adrenocortical hormones

General

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

Secretion

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

Hormone	Details	Stimulus	Effect
Aldosterone	1° mineralocorticoid (95% effect) ½ life 20mins metabolism: liver to tetrahydroglucuronide derivative → excreted in urine regulation: -ve feedback	RAAS: ↑ATII (↓vol, ↓osmolarity) ↑ACTH ↑[K+] Plasma Na ↓pH	**↑NaCl/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 → conjucated 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 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 a1 + b-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
Androgens	testosterone = most active androgen		masculinising, ↑protein anabolism, ↑growth androstenedione → oestrogen in peripheral circulation (fat)

Describe the physiological effects of the glucocorticoids: PAST QUESTION (high fail rate)

General

- glucocorticoids = steroid homrones released from zona fasiculata 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

Physiological effects

- **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
- 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 catehcolamines to exert vasopressor, lipolytic, bronchodilator effects

- Other systems
  - CNS: ↓glucocorticoids → irritability + poor concentration
  - CVS: essential for normal CVS response to stress; ↑response to catecholamines (permissive effect) → +ve inotrope
  - GIT: ↓PG synthesis + ↑acid + pepsin production → ↑peptic ulcers
  - Renal: handling of body water: ↓glucocorticoids → 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 → 2o ↓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

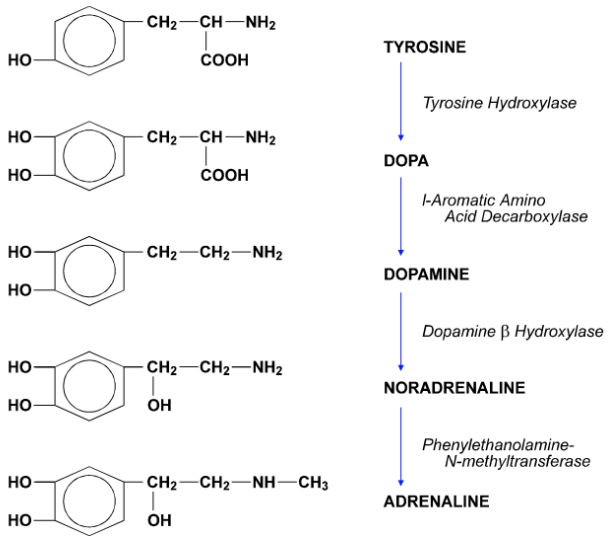
Hormones produced in adrenal medulla = catecholamines:

- adrenaline + noradrenaline
- dopamine

Structure + function of adrenal homrones

- 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



Biosynthesis of catecholamines

- Synthesis in adrenal medulla (modified SY ganglion composed of chromaffin c
- 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 limit
  - DOPA decarboxylated to dopamine
  - Dopamine converted to NAd
  - NAd converted to Ad by *PNMT* (phenylethanolamine N-methyltans

Stimulus:

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

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 miscule
    - 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 → ↑intracellular Ca2+
      - inotropy, chronotromy, dromotropy, renin release
    - β2:
      - skeletal vascular + bronchial smooth muscle, liver, cell membrane

- vasodilation, bronchodilation, hepatic glycogenolysis, ↑activity Na/K ATPase pump → ↑intracellular K

Renin and angiotensin

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

RAAS

- hormone system that regulates BP + water balance in body

Renin

- acid protease; ½ life 80min
- released by granular cells in JGA of kidney
- rate limiting step in RAAS: splits angiotensinogen (produced in liver) to angiotensin I → ATI → ATII by pulmonary ACE
- Release of renin controlled by:
  - SNS
  - Intrarenal baroreceptors
  - Macula densa/ tubuloglomerular feedback
  - ATII
- Factors influencing rate of secretion
  - ↑secretion
    - ↑SNS activity: direct β1 effect
    - ↓pressure on intrarenal baroreceptors
    - ↓Na/↑K content at macula densa (tubuloglom feedback)
    - PGI2, PGE2
  - ↓secretion
    - ATII (-ve feedback)
    - ↑pressure intrarenal baroreceptors
    - ↑Na content at macula densa (tubuloglom feedback)
    - vasopressin (ADH)

Angiotensin II

- Glycoprotein; ½ life 1-2mins
- Effector of RAAS
- Actions via AT1R
  - **↓GFR**
    - mesangial cell constriction → ↓glom SA → ↓Kf → ↓GFR
    - afferent > efferent constriction → ↓GFR
  - **Vasoconstriction**
    - **peripheral** : via AT1R, GPCR Gq: ↑MAP
    - **constricts peritubular capillaries:** → ↓capillary pressure → ↓fluid reabsorption
  - **Tubular absorption**
    - **Direct effect: ↑Na/H2O reabsorption** CD
    - Indirect effect: ↑aldosterone
    - ↑K excretion from CD
  - **central effect**
    - **Stimulate ADH release**
    - **Thirst**
  - **SNS stimulation**
  - **-ve feedback on renin production**

Problems in anaesthetised pt taking ACEI/ ARBs

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

General

- kidneys play role in regulation of body water + electrolytes
- important component = JGA
- JGA
  - 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
  - in walls of distal tubule
  - primary role: tubuloglomerular feedback (autoregulation) through:
    - sensor for flow in DCT
    - production of locally active vasoconstrictor

Atrial natriuretic peptide

	Production	Stimulus	Site of action	Effect
ANP	RA	Atrial stretch (↑CVP)	Efferent + afferent arteriole CD	- dilation afferent arteriole/ constriction efferent arteriole → ↑GFR → ↑H2O, solute filtered. - Inhibit RAAS - ↓ADH - Na absorption proportional to GFR, therefore ↑reabsorption Na → glomerulotubular balance

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 ascLoH and DT

Long term = osteoclast activity via PTH, calcitriol, calcitonin

Hormone	Production	Stimulus	Actions
PTH	In **chief cells** of parathyroid Prehormone → cleaved to prohormone → hormone (ER +golgi)	↓[Ca2+]	↑Ca2+ reabsorption DCT/CD ↓PO4 reabsorption PCT ↑activation of vit D to calcitriol ↑bone resorption/ ↓bone formation → ↑Ca2+ release from bone
Vit D	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)	↓[Ca2+]	↑Ca2+ absorption in small intestine ↑bone reabsorption ↑Ca^{2+} + PO4 reabsorption from PCT
Calcitonin	Secreted from parafollicular cells of thyroid	↑[Ca2+]	inhibit osteoblast activity (↓bone reabsorption) ↑Ca/PO4 excretion ↓calcitriol synthesis ↓jejunal absorption of dietary Ca2+

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

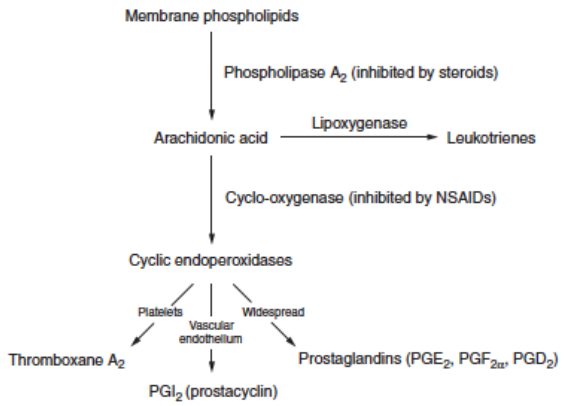


Figure 10.4 Prostaglandin synthesis.

Prostaglandin receptors

- 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

Physiological Roles - ("Multitudinous & varied")

Type	Receptor	Physiological Role
Thromboxane (TXA)	TP	blood clot activation and stabilisation (TXA produced by platelets)
(Prostacyclin) PGI2	IP1, IP2	Vasodilation (important renal vasodilator) inhibition platelet aggregation (most potent) bronchodilatation
PGE2	EP1	bronchoconstriction GI tract smooth muscle contraction
	EP2	bronchodilatation GI tract smooth muscle relaxation vasodilatation → patency of ductus arteriosus
	EP3	↓ gastric acid secretion ↑ gastric mucus secretion uterus contraction (when pregnant) GI tract smooth muscle contraction lipolysis ↑ platelet response to their agonists and ↑ atherothrombosis
	Unspecified	Hyperalgesia pyrogenic Promotes wakefulness
PGF2α	FP	Uterus contraction, bronchoconstriction, pulmonary vasoconstriction, vasoconstriction, GIT muscle constriction
PGD2	DP1, DP2	Promotes sleep, renal vasodilator

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

Metabolic and endocrine - other

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: ↓MAP → ↓cerebral perfusion → confusion, delirium
- CVS:
  - Bacterial endotoxin → cytokine release → vasodilation + ↑vascular permeability → ↓SVR + ↓MAP + oedema
  - ↓MAP → baroreceptor → ↑SNS → ↑HR + ↑CO
  - inflammatory cytokines → myocardial depression
- resp
  - ↑metabolic demand → ↑MV → ↑RR
  - endothelial dysfunction → pulmonary interstitial oedema → V/Q mismatch → hypoxaemia
  - pulmonary oedema/ ARDS
- GIT: Stress ulcers; ↑gut wall permeability → ↑migration of bacteria
- Renal: ↓MAP → ↓RBF → ↓GFR → 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 conseqences

- 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 hypoperfusion → ↓cori cycle → lactaemia
- catabolism + stress response
  - sepsis → catabolic state → depletes stores of glycogen, fat, protein

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

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

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

Components

- Water:
  - Requirement: 30-35ml/kg/day
- Energy in form of CHO + lipids
  - Requirement: 125kg/kg/day
  - Glucose (17kj/g): substrate required by brain + metabolised by all body tissues; prerequisite for protein metabolism
  - Lipids (37kj/g): in form of soybean emulsions; necessary for cell wall intefrity + 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 condction + ECF tonicity
  - K+: 0.7-1mmol/kg/day: membrane potential + ICF tonicity
  - 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)

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 mitochrondria (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 dlivery = 1L O2/min
  - O2 flux/ or total body O2 delivery ↓with age
- 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
  - 0.003 = 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 ↑aveolar membrane thickness + ↓functional surface area
    - ↑WOB
    - anaemia → ↓O2 carrying capacity
    - overall: ↑V/Q mismatch → ↓ability to oxygenate blood when tissue extraction ↑s

ENDOCRINE PHARMACOLOGY

Describe the pharmacology of:

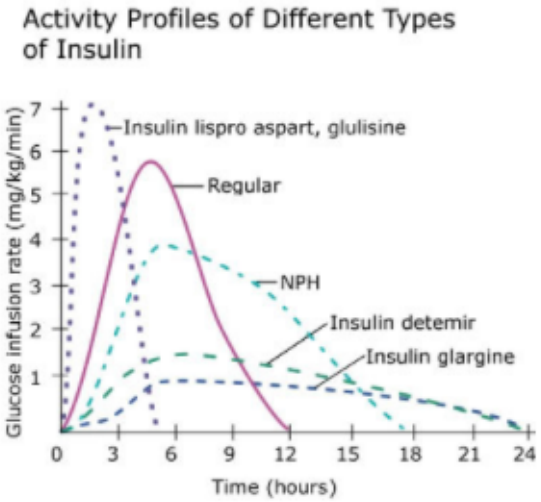
Insulin preparations

	Insulin
Chem	Naturally occurring: polypeptide hormone; synthesised from proinsulin in rough ER of βcells IoL → excreted via exocytosis in response to ↑intracellular [Ca2+] Synthetic: recombinant DNA of bovine/ human recombinant/ porcine insulin
Uses	DM BSL control Hyperkalaemia BB / CCB toxicity
Pres	CCS for injection typically 100U/ml
Action	stimulation of CHO metabolism, protein synthesis, lipogenesis binds to + activates specific membrane bound R → effects mediated by alterations in intracellular concentrations of cyclic nucleotides direct effect on LPL ↑rate of transcriptional and translational events during protein synthesis controls emrbane polarisation + ion transport by activating Na/K/ATPase

Metabolic	- Liver
	  ○ ↑rate of diffusion of glucose into all cells esp. hepatocytes by ↑activity of glucokinase
	  ○ ↑rate of glycogen synthesis by ↑activity of phosphofructokinase + glycogen synthetase
	  ○ inhibits glycogenolysis + gluconeogenesis
	- 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 manufactor of storage TGs
	- Muscle
	  ○ Active transport of aa into cells
	  ○ ↑mRNA translation + DNA transcription
	  ○ inhibits catabolism of proteins

Electrolyte	- ↑rate of K and Mg transport into cells
Toxicity/ SE	
Route/ dose	IM/ IV/ subcut / IVI
A	inactive when administered PO; destroyed by GI proteases
D	little protein binding; Vd 0.075L/kg
M	rapidly metbaolised in the liver, muscle, kidney by glutathione insulin dehydrogenase
E	metabolites in urine; clearance 33.3ml/min/kg (18ml/min/kg in diabetic); elimination ½ life 1.6-3.4mins (5-8mins in diabetic

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



Oral hypoglycaemics

	Sulfonylureas - gliclazide	**Biguanides – metformin**	**Glitazones / thiazolidinediones - pioglitazone**
Chem	S-phenylsylfonylurea structure with substitutions on phenyl ring + urea terminus	Biguanide	Glitazones
Uses	T2DM	T2DM	T2DM
Pres	3 generations - 1st generation: tolbutamide - 2nd generation: gliclazine, glibenclaminde - 3rd generation: glimepiride All tablet form	Tablets: 500/850mg metformin hydrochloride	Tablet
Action	Hypoglycaemia → ↑insulin secretion from pancreatic βcells + may ↑insulin sensitivity binds + inhibits ATP-sensitive K channels on pancreatic βcells → depolarisation → ↓permeability to K → open voltage gated Ca2+ channels → ↑intracellular [Ca2+] → ↑release of insulin vesicles	Delay glucose absorption + ↑peripheral insulin sensitivity **MoA:** - activates AMP activated protein kinase - ↓hepatic gluconeogenesis / glycogenolysis - ↓GIT glucose absorption - ↑peripheral insulin sensitivity - ↑GLP-1 synthesis in ileum	PPARy R inhibition → - ↓hepatic glucose production - ↑hepatic glucose ultilisation - ↓insulin resistance
AS	Cholestasis	Nausea, diarrhoea	
Metab	↓TG, cholesterol FFA	↑sensitivity to peripheral actions of insulin by ↑number fo low affinity binding sites for insulin in RBC, adipocytes, hepatocytes, skeletal muscle Does ***not*** cause hypoglycaemia in diabetic pts	
Other	↓microthrombosis: partial inhibition platelet aggregation + action on vascular endothelium fibrinolytic activity with ↑tissue plasminogen activator activity		
Toxicity/ SE	↑appetite, weight gain hypoglycaemia leucopenia/ thrombocytopenia / teratogenic	Lactic acidosis: - inhibition of enzymes involved in aerobic glucose metabolism: ↑anaerobic metabolism → ↑lactate production. Usually lactate quickly converted back to glucose via GNG - inhibition of GNG enzymes GI upset	Weight gain; fluid retention; hepatic dysfunction
Route/ dose	PO: 40-160mg BD	PO: 500-2g BD	15-30mg daily
Onset	Glimepiride: onset 1 hr; max effect 2-4hr Tolbutamide: onset 1hr; max effect 5-8hr	Regular release: 2-3hr Extended release: 4-8hr	Peak plasma time 2-4hr
Duration	Glimepiride: 24hr Tolbutamide: 6-24hr		24hr
A	Bioavailability 80-100%	Bioavailability 60%	High bioavailability Delayed onset + late peak given MoA
D	99% bound to albumin VD: - glicladie 0.4L/kg - glibenclamide 0.15L/kg - glimepiride 0.12L/kg	Minimally/ nil PB	Low Vd: 0.6L/kg
M	Extensive hepatic metabolism via CYP2C9 to inactive metabolites	Not metabolised	Extensive hepatic phase 1 to inactive + active metabolites
E	30-50% renal faeces ½ life gliclazide 12-20hrs; glibenclamide 1-2hr; glimepiride 5-8hr	Renal excreted unchanged in urine Clearance > GFR = active secretion Elimination ½ life 2-5hrs	Renal and GI elimination of active + inactive metbaolites
Special points	Crosses placenta → foetal hypoglycaemia	CI in renal impairment due to ↑risk lactic acidosis	

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

Common Types of Hypoglycaemic Agents

Group	Mechanism of Action
Exogenous insulin *human insulin rys (Actrapid) – short* *insulin aspart (Novorapid) – short* *insulin glargine (Lantus) – long*	Acts on insulin receptor → tyrosine kinase receptor → autophosphorylation → intracellular signalling cascade → ↑MAPK → ↑MAP → alters gene transcription ***S/fx*** – hypoglycaemia, lipodystrophy at injection site, allergic reactions
Sulphonylurea *(e.g. gliclazide, glibenclamide)*	Binds and inhibits ATP-sensitive K^+ channels on pancreatic β cells → depolarisation → open voltage-gated Ca^{2+} channels → ↑intracellular $[Ca^{2+}]$ → ↑release of insulin vesicles ***S/fx*** – hypoglycaemia, GIT upset
Biguanides *(e.g. metformin)*	Activates AMP-activated protein kinase (AMPK) + other mechanisms resulting in: (1) decrease hepatic gluconeogenesis (2) decrease hepatic glycogenolysis (3) decreases GIT glucose absorption (4) increase peripheral insulin sensitivity (5) enhances GLP-1 synthesis in ileum ***S/fx*** – lactic acidosis (esp. hepatic + renal dysfunction), GIT upset Metformin inhibits complex I of electron transport chain → anaerobic metabolism of glucose → lactate production
Thiazolidinediones *(e.g. rosiglitazone, pioglitazone)*	PPAR-γ receptor inhibition resulting in: (1) ↓hepatic glucose production (2) ↑hepatic glucose utilisation (3) ↓insulin resistance ***S/fx*** – weight gain, fluid retention, hepatic dysfunction
Alpha-glucosidase inhibitors *(e.g. acarbose)*	Inhibit intestinal α-glucosidase → ↓carbohydrate breakdown in GIT → ↓carbohydrate absorption ***S/fx*** – undigested carbohydrate in GIT → cramps + diarrhoea
Dipeptidyl peptidase-4 inhibitor *(eg. sitagliptin, vildagliptin)*	Competitive antagonist at DPP-4 → prevent GLP-1 and GIP inactivation → ↑insulin secretion and ↓glucagon secretion ***S/fx*** – less hypoglycaemia
Glucagon-like peptide-1 agonists *(e.g. exenatide)*	Mimics effect of GLP-1 → multiple mechanisms: (1) increase insulin secretion (2) suppress glucagon secretion (3) reduce gastric emptying (4) reduce satiety ***S/fx*** – hypoglycaemia, nausea/vomiting
Meglitinides *(e.g. repaglinide)*	similar mechanism to sulphonylureas ***S/fx*** – hypoglycaemia

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 lipcortins
  - 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 a1 + b-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+ excretin
    - NB In large dose: inhibits endogenous adrenal cortical secretion, thymic activity, and ACTH excretion
    - Aldosterone:
      - **↑NaCl/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 weakenss/ steroid myopathy / HTN / PUD, pancreatitis, oesophagitis

	Hydrocortisone	Prednisolone	Methylprednisolone	Dexamethasone	Fludrocortisone
Chem	Glucocorticosteroid	Synthetic glucocorticosteroid	Synthetic glucocorticoid	Synthetic glucocorticosteroid	Synthetid mineralocorticoid
Pres	Tablets: 10/20mg Vials: white lyophilized powder diluted in water → 100mg of hydrocortisone sodium succinate Topical creams	Tablets: 1 / 2.5 / 5 / 20mg Solution for injection 25mg/ml prednisolone acetate drops	Tablets: 2/4/8/16/32 Injectable suspension 20/40/80mg/ml Powder for injection: 40/125/500/1g/2g	Tablets 0.5/2mg/ oral solution IV dexamethasone sodium phosphate 3.8mg/ml Topical creams	Mineralocorticoid replacement in primary adrenal insufficiency Salt losing CAH Orthostatic hypotension
Relative DE	100mg	25mg	20mg	4mg	
Route/ dose	IV: 100-500mg 6-8hrly PO: 10-20mg/day	PO: 5-60mg/day	PO/ IV/ IM	PO 1-9mg IV:	PO: 50-100microg daily
Onset	<2hrs	IV: 5min / PO: 1hr	PO: 1-2hr	IV <5min	Peak plasma time <1.5hr
Duration	8hrs	18-36hr	PO:36hr IM: 1-4weeks		1-2 days
A	PO: bioavailabilty 50%	PO: bioavailabilty 80-100%		70% protein bound; high uptake in liver, kidney, adrenals	Bioavailability 100%
D	Variable PB depending on conc Reversibly bound to alb (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 concs: 90% protein bound High conc: 60% protein bound Vd 0.3-0.7L/kg according to dose	Vd 1L/kg	**Liver**	40% PB
M	Liver To tetrahydrocortisone	Liver Hydroxylation → conjugation	Liver	**Urine** plasma ½ life 4hrs biological ½ life 50hrs	Liver
E	Clearance dose dependent: 150-250ml/min Elimination ½ life 2hrs	11-14% unchanged in urine 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	¼ as potent as predisolone	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 mineralo corticoid 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 ↓risk PONV; requires single dose only
- Anti-inflammatory/ immunosuppressive:
  - Prevent inflammatory response
  - ↓vascular permeability/ proliferation, ↓oedema
  - ↓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

Outline the pharmacology of:

Thyroid hormone replacement and anti-thyroid drugs

	Thyroxine	**Propylthiouracil**	**Carbimazole**
Chem	Iodine containing amino acid derivatives of thyronine		Imidazole
Uses	Hypothyroidism Myxedema coma Goiter	Hyperthyroidism: graves disease Thyrotoxic crisis	Hyperthyroidism Thyrotoxicosis
Pres	Tablets: 25/50/100microg levothyroxine sodium		
Action	Modulation of growth + metabolism MoA: thyroid homones combine with receptor protein within cell nucleus→ activate DNA transcription → ↑rate RNA synthesis + ↑protein synthesis	Inhibits synthesis of thyroid hormone by blocking oxidation of iodine in thyroid gland	Anithtyroid action due to conversion to **methimazole** ↓uptake + concentration of inorganic iodine by thyroid ↓formation of di-iodotyrosin and thyroxine methimazole prevents thyroid peroxidase enzyme from coupling + iodinating tyrosine residues on thyroglobulin → ↓T3 + ↓T4
CNS	↑excitability, seizures, tremor		
CVS	↑HR, ↑inotropy, ↑CO, ↓SVR, ↓DBP		
Resp	↑MV due to ↑CO2 production		
MSK	↑OB activity		
Metab	↑BMR up to 100% ↑CHO metabolism (↑glucose uptake, ↑glycolysis, ↑gluconeogenesis) ↑fat metabolism (↑lipolysis, ↑non shivering thermogenesis, ↓plasma cholesterol, ↓plasma phospholipids, ↓TGs) ↑protein metabolism (↑anabolism at physiological levels, ↑catabolism at high levels)		
Toxicity/ SE	Thyrotoxicosis	Hepatitis	Nausea,
Route/ dose	PO: 25-300microg daily divided doses titrated to response IV	PO: 50-150mg q8hr up to 300mg 4-6hr in crisis	
Onset	24hr to onset; peak effect in 6-7days	Peak effect 1-2hr	
Duration		12-24hr	
A	100% absorption	80% PB	85% protein bound
D	Bound to thyroid binding lgobulin and thyroid binding pre albumin in plasma >99% VD levothyroxine 0.2L/kg VDT3 0.5L/kg	VD 0.4L/kg	
M	33% levothyroxine converted to triidothyronine in periphery (lver and kidney) + rT3 → conjugation to glucuronide + sulfate	Liver to glucuronide conjugates, inorganic sulfates, sulfur metabolites	
E	20-40% in faeces unchanged clearance of levothyroxine 1.7ml/kg/min; elimination ½ life 6-7days clearance of T3: 17ml/min; elimination ½ life 2 days	Urine 35% Elimination ½ life 102hr Clearance 7L/hr	
Special points	↑anticoagulant activity of warfarin B blockers interfere with the conversion of levothyroxine to T3 → ↑inactive rT3		

Glucagon, Vasopressin and analogues

	Glucagon	Vasopressin (ADH)	terlipressin	Desmopressin (DDAVP)
Chem	Polypeptide hormone extracted from αcells of pancreatic islets of langerhans	Synthetic nonapeptide analogue of endogenous arginine vasopressin (ADH) Synthetic vasopressin = "argipressin"	Vasopressin analogue	Synthetic analogue of vasopressin
Uses	Hypoglycaemia Radiological investigation of GIT Cardiogenic shock Propranolol overdose	Diabetes insipidus Uncontrolled haemorrhage with oesophageal varices Catecholamine refractory septic shock	Bleeding oesophageal varices Hepatorenal syndrome type 1 in pts considered for transplant	Central diabetes insipidus Haemophilia A / vWD platelet dysfunction
Pres	Vials 1/10mg lyophilized glucagon hydrochloride with lactose → reconstituted in glucerol + water prior to use Prefilled syringes 1mg glucagon	Terlipressin: CCS Desmopressin: oral lyophilizate	CCS	White powder
Action	Acts via cell membrane receptors which stimulate AC activity → ↑intracellular [cAMP] Final effects mediated via cascade of protein kinases	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 Some oxytocin effects	**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 activaton **Antidiuretic**: ↑water permeability in renal tubular cells → ↓urine vol + ↑urine osmolality
CVS	**+ve inotrope** +ve chronotrope no ↑myocardial irritability relaxation of smooth muscle	↑MAP 2o vasoconstriction (V1) → ↑SVR coronary artery vasoconstriction → angina, MI, VT/VF	Vasoconstriction via V1 Rs on vascular smooth muscle in splanchnic + portal circulation ↑SVR + reflex ↓HR Some V2 effects	Lacks vasoconstrictor effects due to minimal V1 agonism Haemostatic agent Platelet dysfunction: ?↑vWF → ↑platelet adhesion
AS	↓tone in GIT inhibit pancreatic + gastric secretions ↓ureteric tone			Doesn't cause ↑uterine tone due to ↓V1 agonism
Metab	↑gluconeogenesis/ glycogenolysis / ↑BSL ↑lipolysis / ↑ketogenesis ↑proteolysis stimulates release of endogenous catecholamines			
Other	small ↑UO + RBF	↑vWF; ↑uterine contraction		Antidiuretic: act on renal CT to ↑permeability to water reabsorption Effect of FVIII: ↑FVIII coagulant activity + vWF
Tox/ SE	Hypokalaemia (2o ↑insulin secretion); N+V+D	↓cutaneous + splanchnic perfusion	Headache/ bradycardia/ hypokalaemia/ ↓Mg/ ↑QT	Mild tachycardia, flushing, headache Hyponatramiea (2° antidiuretic effect) Rare: arterial thrombotic events
Route/ dose	IV/ IM/ SC 1-5mg IVI: 1-20mg/hr	IV: 0.04 units/min DDAVP: 4-8microg PO/ SL/ nasal	IVI only Varices: 1.7mg 4hrly	PO/ intranasal / IV IV/ subcut: 0.03microg/kg q12-24hr
Onset	IV: <1 min; SC 8min	Minutes	Peak plasma concentration 60-120min	IV 30 min
Duration	↑BSL lasts 10-30mins	Up to 6 hours		6-14hr
A	Inactive when PO	Poor PO bioavailability		PO bioavailability 5% (compared to intranasal)
D		Not protein bound Vd 0.14L/kg		Similar to ADH; nil info on PB
M	Degraded by proteolysis by splanchnic, hepatic, renal routes	Vasopressinases (peptidases to amino acids) ½ life 10-20mins	peptidases	?
E	Clearance 8-12ml/kg/min Elimination ½ life 3-6mins	Recycled into aa pool	Elimination ½ life 40mins 1% unchanged in urine	Urine
Special points	Clearance ½ in pts with renal failure Not removed by haemodialysis Potentiates anticoagulant effect of warfarin			