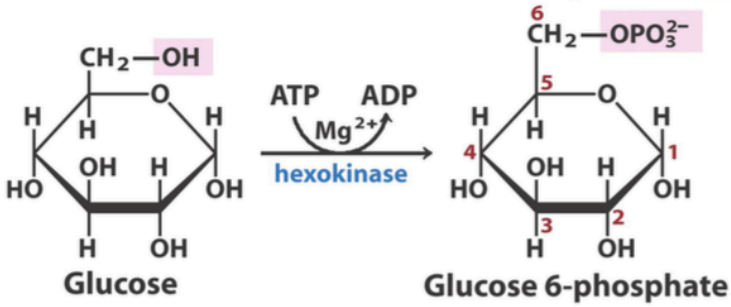
- This chemical reaction must be shielded from water to keep the phosphate from being cleaved off ATP by a water molecule
- Hexokinase performs an induced fit, closing around ATP and glucose once they are bound

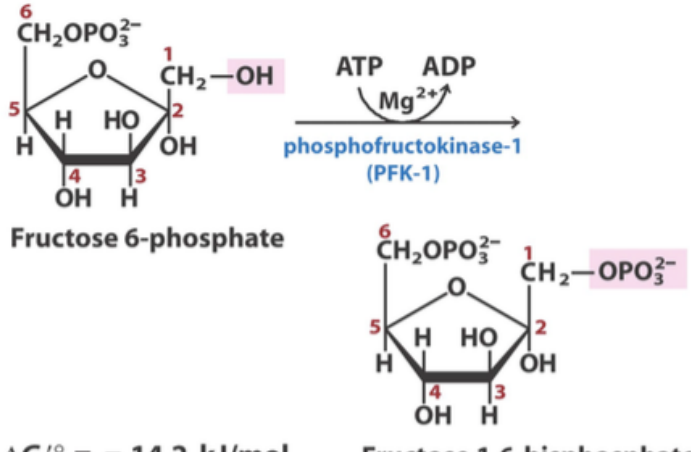
Reaction ❶: Phosphorylation of glucose

Page 548 of Lehninger



$\Delta G'^{\circ} = -16.7$ kJ/mol

- Reaction 2 – Conversion of glucose-6-phosphate → fructose-6-phosphate
  - Isomerization – A reaction that changes the shape of a single molecule but doesn't permanently add or remove any atoms
  - Isomer – Same number of atoms, different arrangement
  - Fructose has a 5 atom ring structure, glucose has 6 atom ring
    - No atoms gained/lost
- Reaction 3 – Phosphorylation of fructose-6-phosphate → fructose-1,6-bisphosphate (F-1,6-BP)*** EXAM QUESTION
  - Pi from ATP transferred to sugar → F-1,6-BP
    - Phosphate molecules attached to two different points (1st and 6th carbons)
  - Phosphofructokinase-1 (PFK1) is the gatekeeper of glycolysis → Catalyses the committed step of the glycolytic pathway
  - PFK1 proposed to have important roles in metabolic reprogramming in cancer
  - Somatic cancer mutations of PFK alter enzymatic activity and allosteric regulation
  - Regulated allosterically
  - PFK1 is a bacterial enzyme with 4 identical subunits. The active site binds to the sugar and ATP. The enzyme also has regulatory binding sites at the top and bottom



$\Delta G'^{\circ} = -14.2$ kJ/mol

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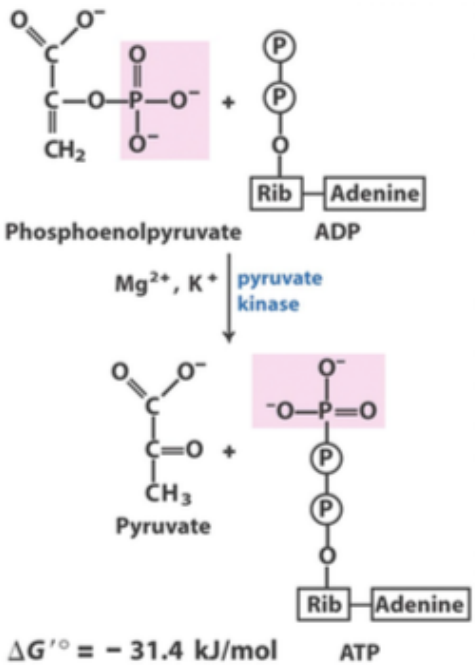
Page 9 of 105

- Reaction 4 – Cleavage of fructose-1,6-biphosphate (F-1,6-BP)
  - Aldolase splits sugar into two 3 carbon molecules
    - Dihydroxyacetone phosphate
    - Glyceraldehyde 3-phosphate
- Reaction 5 – Interconversion of the triose phosphates
  - Triose phosphate isomerase (enzyme) rearranges atoms of dihydroxyacetone phosphate into glyceraldehyde 3-phosphate (end up with 2 equivalents of glyceraldehyde 3-phosphate)
  - The TIM barrel (structure that occurs widely in nature) is a conserved protein fold of triose phosphate isomerase. The TIM barrel consists of eight alpha-helices and eight parallel beta-strands that alternate along the peptide backbone
- Reaction 6 – Oxidation of glyceraldehyde-3-phosphate (G-3-P) to 1,3-bisphosphoglycerate (1,3-BPG)
  - Glyceraldehyde 3-phosphate dehydrogenase attaches an inorganic phosphate to glyceraldehyde 3-phosphate → 1,3-biphosphoglycerate
  - NAD+ is a cofactor here
  - NADH produced is often called a reducing equivalent and is used in the TCA cycle
    - Electrons passed to NAD+ to produce NADH
  - NAD+ must be regenerated
- Reaction 7 – Phosphoryl transfer from 1,3-biphosphoglycerate (1,3-BPG) to ADP → PAYOFF PHASE (Produces ATP)
  - Phosphoglycerate kinase (enzyme) uses one molecule ADP to produce 3-phosphoglycerate + ATP
  - Reversible reaction (important in gluconeogenesis)
  - Produces ATP from ADP
  - 1 glucose molecule → 2 equivalents 1,3-bisphosphoglycerate (therefore 1 glucose → 2 ATP)
- Reaction 8 – Conversion of 3-phosphoglycerate (3-PG) to 2-phosphoglycerate
  - Phosphoglycerate mutase (enzyme) isomerases 3-phosphoglycerate to 2-phosphoglycerate (phosphate moves carbons)
  - Isomerization reaction
- Reaction 9 – Dehydration of 2-phosphoglycerate to phosphoenolpyruvate (PEP)
  - Enolase strips H2O molecule from 2-phosphoglycerate → phosphoenolypyruvate
  - Phosphoenolpyruvate now has double bond
- Reaction 10 – Transfer of phosphoryl group from phosphoenolpyruvate (PEP) to ADP → PAYOFF STEP
  - Pyruvate kinase uses ADP to produce pyruvate + ATP



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Page 10 of 105

    - Decrease in translocation of H+
    - Collapse of proton motive force
        - ATP synthase can potentially operate in reverse
        - Can hydrolyse ATP under hypoxic conditions (dangerous if you need to conserve ATP)
- Hydrolysis of ATP by ATP synthase is prevented by a small protein inhibitor (IF1)
    - Inhibitor of the F1 subunit (catalytic subunit of ATP synthase)
    - Simultaneously binds 2 synthase molecules together inhibiting their activity
    - Only active as a dimer at lower pH (high H+)
    - When cell relies upon glycolysis for ATP, concentrations of pyruvic and lactic acid increase

Hypoxia leads to ROS production (reactive oxygen species)

- In hypoxic conditions there is an imbalance between electron supply and transfer to O2
    - Leads to an increase in ROS (reactive oxygen species), particularly O2. (which carries an unpaired electron and is therefore a radical)
    - Production of O2 is related to the concentration of potential electron donors, the local concentration of O2
- Regulation via hypoxia inducible transcription factor 1 (HIF1)
    - Regulation of PDH via PDH-kinase
        - HIF-1 increases synthesis of PDH kinase -> Phosphorylation of PDH -> inactive
        - Regulates entry into TCA during hypoxia
        - Slows NADH and FADH2 production slowing supply of electrons to the respiratory chain
    - Regulation of complex IV (cytochrome oxidase)
        - HIF-1 increases synthesis of a protease that degrades a subunit of complex IV (COX4-1)
        - Triggers synthesis of alternate subunit (COX4-2) which is specifically suited to hypoxic conditions
    - Also up-regulates glucose transporters and glycolytic enzymes

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Page 30 of 105

Summary

- BE ABLE TO DRAW GLUCOSE, G6P, PYRUVATE AND LACTIC ACID
- PDH complex regulated allosterically and by phosphorylation
- Products of the TCA cycle (NADH and ATP) affect all regulated enzymes in the cycle
- Coupling can be observed using an oxygen electrode and by measuring ATP production
- Oxidative phosphorylation can be uncoupled in vitro by various uncoupling reagents and in vivo by uncoupling proteins
- Uncoupling protein 1 (UCP1) is found in some animals, human infants
- In hypoxia there is an imbalance between electron supply and transfer to O2 leading to ROS production

- Pyruvate
- Lactate
- Certain amino acids
- Glycerol → Dihydroxyacetone phosphate (intermediate of TCA)
    - Both 3C compounds

Lactate

- Result of glycolysis in erythrocytes and anaerobic muscle during vigorous exercise
- NADH produced by lactate dehydrogenase in the cytosol (recycling NADH)
- Allows us to cycle glucose to lactate and the lactate can be converted back to glucose in the liver (the glucose can re-enter the blood stream and be taken up by working muscle)
- The cori cycle
    - Lactate carried in the blood to the liver where it is converted back to glucose during recovery from strenuous exercise

Amino acids

- Sources for gluconeogenesis include AA and glycerol from FA (can be converted into glucose)
- Some AA give rise to pyruvate which can be used in gluconeogenesis (used to generate glucose)
- Glucogenic and ketogenic amino acids depending where they enter gluconeogenesis
- Alpha-ketoglutarate, succinyl CoA and fumarate are all citric acid cycle intermediates and give rise to oxaloacetate
    - Amino acids can feed into the TCA cycle at more than one point
    - We can't make net conversions of acetyl CoA into glucose → It can feed into Krebs cycle but in order to incorporate acetyl CoA into the cycle we require a molecule of oxaloacetate → Lose 2 carbon equivalents so no net glucose
        - Some plants by pass the loss of CO2 equivalents and can there for use acetyl CoA to make glucose
        - In starvation we cannot use the FA to make glucose (Cant make acetyl CoA into glucose)

Precursors of gluconeogenesis

- Beta oxidation of fatty acids gives rise to acetyl CoA (cannot make net glucose from Acetyl CoA, but pyruvate we can via gluconeogenesis)
- Pyruvate resulting from glycolysis can be converted to acetyl CoA by pyruvate dehydrogenase reaction (irreversible)
    - Once at acetyl CoA it is irreversible

Glycerol

- Glycerol resulting from the hydrolysis of triacylglycerols can be used in gluconeogenesis

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Page 34 of 105

- F26BP not a glycolytic intermediate but is essential for regulation
- A regulator specifically produced to regulate glycolysis and gluconeogenesis
- Levels of F26BP important for regulating glycolysis
    - Inhibit FBPase-1
    - Upregulates PFK1
- F26BP is synthesised from F6P by PFK-2
- Broken down by fructose-2,6-bisphosphate (FBPase-2)

Regulation by F26BP

- Has opposite regulatory effects on glycolysis and gluconeogenesis
- F26BP allosterically regulates fructose-1,6-bisphosphatase in a similar manner
    - Activates phosphofructokinase (glycolysis)
    - Inhibits fructose-1,6-bisphosphatase (gluconeogenesis)
- When F26BP binds to its allosteric site on FBPase-1
    - Decreases the enzymes affinity for F6P
    - Inhibited by as little as 1uM F26BP
    - Increases FBPase-1 sensitivity to AMP
- When F26BP binds to its allosteric site on PFK-1
    - Increases the enzymes affinity for F6P
    - Decreases the enzymes affinity for ATP

Regulation of F26BP levels

- PFK2 and FBPase-2 are enzymes on the same protein
    - Make the same non-glycolytic intermediate F26BP
- High BG → Insulin binds to cell surface → Tyr phosphorylation → Activates PFK2 → F26BP → Activates PFK-1 → Glycolysis
  Low BG (want to shut down glycolysis) → Glucagon → Signalling cascade resulting in phosphorylation of cAMP → FBPase-2
- Increased F26BP stimulates glycolysis inhibits glucongeogenesis
- Decreased F26BP inhibits glycolysis and stimulates gluconeogenesis

Summary

- Gluconeogenesis is the synthesis of glucose from non-carbohydrate precursors
    - Pyruvate, lactate, amino acids and glycerol (but not fatty acids in animals)
- Gluconeogenesis and glycolysis share 7 common steps, but not those that are irreversible
    - Hexokinase (step 1)
    - PFK-1 (step 3)
    - Pyruvate kinase (step 10)
        - These reactions are bypassed by 4 different enzymes
            - Pyruvate carboxylase
            - PEP carboxykinase
            - Glucose-6-phosphatase
            - Frcutose-1,6-bisphosphatase

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Page 36 of 105

- When BG levels are high insulin stimulates glycogen synthesis by inactivation of glycogen synthase kinase 3
- Glycogen synthase kinase phosphorylates glycogen synthase (inactive)
- Phosphatase activates glycogen synthase
- Inactivation of glycogen synthase kinase allows PP1 to dephosphorylate and activate glycogen synthase

Phosphoprotein phosphatase 1 is central to glycogen metabolism

- PP1 can remove phosphoryl groups from all three enzymes phosphorylated in response to glucagon/epinephrine
    - Phosphorylase kinase
    - Glycogen phosphorylase
    - Glycogen synthase
- PP1 Is tightly bound to its targets via glycogen targeting protein (Gm)
    - Binds glycogen and above 3 enzymes
- PP1 is itself subject to covalent and allosteric regulation

These allosteric and hormonal signals coordinate carbohydrate metabolism globally

Summary

- Glycogen is a polymer of alpha (1-4) linked subunits of glucose, with alpha (1-6) linked branches constructed around a core primer based on the enzyme glycogenin
- Glucose 6 phosphate is converted to glucose-1-phosphate by phosphoglucomutase (reversibly), before activation via the addition of a nucleotide, forming UDP-glucose – the building block of glycogen
- Glycogen branching and debranching enzymes are responsible for forming and degrading (remodelling the alpha (1-6) linked branches
- Epinephrine and glucagon induce glycogen breakdown (via phosphorylase kinase which phosphorylates/activates phosphorylase) and impair glycogen synthesis (via phosphorylating/inactivating glycogen synthase)
- Insulin and the availability of glucose induces glycogen synthesis, with phosphoprotein phosphatase 1 (PP1) dephosphorylating/activating glycogen synthase, and dephosphorylating/inactivating phosphorylase

Type I diabetes

- Results from the autoimmune destruction of the insulin producing beta cells in the pancreas
    - Cells destroyed by autoimmune processes
    - Glucose metabolism limited
- Manifests itself in childhood (juvenile diabetes)
- Metabolism of glucose is limited by the rate of uptake; glucose uptake is deficient in type I diabetes
- Classical symptoms
    - Polyuria (frequent urination)
    - Polydipsia (increased thirst)

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Page 42 of 105

    - Polyphagia (increased hunger)
    - Weight loss
- BG builds up to high levels → Increased urination → Increased thirst
- Cells unable to take up glucose → Increased hunger

Glucose uptake
- Mediated by GLUT transporters
- In some cells GLUT transporters are always present
    - GLUT1 (ubiquitous; in all cell types)
    - GLUT2 (liver)
    - GLUT3 (brain)
        - Always expressed → Brain reliant on glucose as an energy source
        - Other transporters are regulated
- In skeletal muscle, cardiac muscle and adipose tissue, GLUT4 is sequestered in vesicles and moves to the plasma membrane in response to insulin
    - Recruited into membrane under insulin signal

Effects of type I diabetes on CHO and fat metabolism
- Pancreas fails to secrete insulin
- Insulin receptor not activated
- Failure to recruit GLUT4 transporters in membrane (in skeletal muscle, cardiac muscle and adipose tissue)
- Glucose not taken up by cells
- Insufficient glycolysis (due to insufficient glucose)
- Insufficient TCA cycle and oxidative phosphorylation
- Triglyceride breakdown and fatty acid oxidation

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Page 43 of 105

Inborn errors of metabolism
- Rare genetic disorders that affect enzymes in metabolism
- Gene mutations → Individual enzymes affected
- Body cannot properly turn food into energy (enzymes defective)
- Usually caused by defects in specific proteins (enzymes) that help break down (metabolise) parts of food

Glycolysis in disease
- Glycolytic mutations are relatively rare due to importance of this pathway (produces pyruvate for TCA and precursors for other biosynthetic pathways)
- Majority of mutations in enzymes → Cells cant respire → Cell death

Pyruvate kinase deficiency
- Final step of glycolysis (phosphoenolpyruvate + ADP → Pyruvate + ATP)
- Erythrocytes (RBCs) obtain all their ATP from glycolysis
- A deficiency in pyruvate kinase (PK) results in erythrocytes with decreased energy

- During reperfusion succinate is consumed → Too much QH2 produced → Drives reverse electron transport at complex I → Drives ROS production at complex I → Cell damage

Summary

- Type I diabetes results from inability to produce insulin
- Type I diabetes impacts on glucose uptake by skeletal, cardiac, muscle and fat cells
- Inborn errors in glycolytic enzymes are rare but found
- Mitochondrial diseases are a group of diseases resulting from mutation of proteins important in electron transport and other processes in the mitochondria
    - Leber's hereditary optic neuropathy
    - Leigh syndrome
    - MERRF sundrome
- Other inborn errors in metabolism include fructose bisphosphate deficiency and glycogen storage diseases
- At high altitude, O2 deficiency can lead to increased HR, brain swelling, leakage of blood vessels of alveolar sacs of lung and death
- HR leads to O2 deficiency, rapid depletion of ATP and energy stores and breakdown in osmotic balance of cells

Pentose phosphate pathway

- Produces NADPH and ribose-5-phosphate
    - NADPH similar in chemical properties to NADH (source of reducing power)
    - NADH occurs in oxidative and energy metabolism, NADPH electron donor in biosynthesis
- Required for reducing power and nucleotide precursors
- NADPH is an electron donor
    - Reductive biosynthesis of fatty acids and steroids
    - Repair of oxidative damage
- Ribose-5-phosphate is a biosynthetic precursor of nucleotides
    - Used in DNA and RNA synthesis
    - Used in synthesis of some coenzymes (eg Coenzyme A)
    - We need ribose to make NAD and NADP (cofactors)
    - Ribose at the heart of ATP
    - Ribose linked to phosphates and base in RNA
        - Ribose in RNA has an extra OH at C2
        - Deoxyribose in DNA does not → Increased flexibility

NADPH vs. NADH

- Both have nicotinamide
- Difference is the presence of a phosphate group in NADPH
- Both dinucleotide molecules are able to act as electron donors; they act as cofactors in many biochemical reactions
- NADPH is especially important for reactions involving reduction; the pentose phosphate pathway is the major source of NADPH

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Page 47 of 105

- NADPH oxidised to NADP+
- NADH oxidised to NAD+
- NADH involved in glycolysis, TCA
- NADPH used in biosynthetic pathways and protection from oxidation
- Major source of NADPH is the PPP

Four major pathways of glucose utilisation

- Glucose can be oxidised via pentose phosphate pathway → Ribose-5-phosphate
- Glycolysis (glucose oxidised → pyruvate)
- Glucose stored as glycogen

Glycolysis

- Mutations in glycolytic enzymes rare as glycolysis is central
- The intermediates are required for the biosynthesis of several important compounds
- Step 1 – Glucose → G6P
    - G6P intermediate can enter the PPP → Ribose-5-phosphate
- Step 3 – F6P → F16BP (via PFK1)
- Step 10 – PEP → Pyruvate

Pentose phosphate pathway

- Oxidative and non-oxidative phases
- G6P can be oxidised to 6-phosphogluconolactone (via glucose-6-phosphate dehydrogenase) and NADP+ is reduced to NADPH
- 6-phosphogluconolactone → 6-phosphogluconate (via 6-phosphogluconolactonase)
- The NADPH is used by glutathione reductase to protect cells from oxidative damage and detoxify reactions (GSSG → 2GSH)
- 6-phosphogluconate de-carboxylated (loss of CO2) to ribulose-5-phosphate (via 6-phosphogluconate dehydrogenase) and another NADPH equivalent produced
- Ribulose-5-phosphate → Ribose-5-phosphate (via ribulose-5-phosphate isomerase)
- Ribose-5-phosphate → Nucleotides, coenzymes, RNA, DNA

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Page 48 of 105

What is the NADPH used for?

- In cells that are directly exposed to O2 (lens, cornea, erythrocytes), the NADPH generated by the PPP creates a reducing environment that protects these tissues from free radicals

Glutathione and the PPP

- Glutathione is a tri-peptide consisting of glutamate, cysteine and glycine
- Gutamate joined to cysteine via its side chain
- Cysteine contains SH and is linked to glycine
- NADPH produced by the PPP allows oxidised glutathione to be regenerated to its reduced form (GSH)

- Primaquine and compounds found in fava beans lead to increased amounts of peroxides and other reactive oxygen species (cause oxidative damage)
- If people with G6PD deficiency eat fava beans → Deficient in G6P dehydrogenase → Not enough NADPH → Oxidative stress → Hydroxyl radicals
    - Erythrocytes lyse
    - Haemoglobin is released into the blood
    - Jaundice and kidney failure can result
- G6PD deficiency impairs the ability of red blood cells to maintain their levels of reduced glutathione and therefore their ability to deal with oxidative stress

What happens in the erythrocytes?

- Hemoglobin (Fe2+) → oxidation → Methaemoglobin (Fe3+)
    - In order to carry O2, the heme iron must be 2+
    - Methaemoglobin cannot carry oxygen
    - If we are able to make NADPH we can reduce Fe3+ to Fe2+
- Methaemoglobin signifies damage, cells destroyed

Summary

- The PPP is a process by which cells can generate reducing power (NADPH) that is needed for
    - The biosynthesis of various compounds
    - Reduction of oxidised glutathione
- Produces ribose-5-phosphate
- The non-oxidative phase of the PPP can convert pentose phosphates back to G6P and other glycolytic intermediates
- A deficiency in the first enzyme in the pathway (glucose 6 phosphate dehydrogenase) leads to a decreased amount of reduced glutathione, and increased susceptibility to oxidative damage, particularly in erythrocytes (red blood cells)

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Page 50 of 105

Revision

- GSH (glutathione)
    - Gamma-glutamate + cysteine + glycine
    - SH group from cysteine
- Peroxidase reaction (H_2O_2 (hydrogen peroxide) → H_2O) via the reducing power of glutathione
    - $H_2O_2 + H^+ + 2e^- \rightarrow 2H_2O$
- Glutathione S-transferase takes glutathione and conjugates it to various toxins with nucleophilic centres
    - By conjugating a toxic molecule to glutathione it becomes more soluble and the body can then remove compounds conjugated to glutathione from the cell

Nitrogen metabolism: Amino acids

- Roles of amino acids
    - Energy production

- High fat/protein diet thought to reduce appetite and overall consumption
- Metabolism is similar to fasting but following result
    - Decreased glucose
    - Increased ketones (secreted in breath and urine → net calorie loss)
    - Increased serum lipids
    - Increased NH4+ (hyperammonia)
- Potential health risks
    - Hypoglycaemia causing neural effects
    - Ketoacidosis causing acidification of blood
    - High serum lipids causing heart disease
    - Increased ammonia causing liver damage

Revision

- AA can be classified as 2 groups in AA degradation
    - Ketogenic AA
    - Glucogenic AA
- Most AA do not directly enter into the TCA cycle
- The enzyme defective in phenylketonuria (PKU) is phenylalanine hydroxylase
- The main storage site of protein in the body is muscle
- A key problem of starvation diets is muscle protein loss
- 4 key problems with high protein diets
    - Decreased glucose (hypoglycaemia)
    - Increased NH4+
    - Increased ketone bodies (ketoacidosis)
    - Hyperlipidemia (serum lipids)

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Page 62 of 105

DIETARY AND CIRCULATING LIPIDS

- Lipids have important functions
    - Provide energy source
    - Insulation
    - Reserves of FA which can be released and used as an energy source
    - Energy storage
    - Phospholipids/glycolipids important in cell membranes
    - Glycolipids also involved in trafficking cells around the body (eg blood cells)
- Main lipids
    - Fatty acids
    - Triacylglycerols
    - Phospholipids
    - Glycolipids
    - Lipid hormones (vitamins etc)
    - Pigments

Lipids revision

Triacylglycerol

- Glycerol backbone

- Genetic disorder
- Absence or deficiency in LDL receptors
- Macrophages engulf LDLs and swell to form foam cells (rich in fat) → Form cholesterol plaques which block blood vessels
- 4 fold higher plasma cholesterol and LDL concentrations
- Excess blood LDL is oxidised and engulfed by macrophages to form foam cells and atherosclerotic plaques in blood vessels
- Homozygotes (both genes affected) die of coronary heart disease in childhood unless treated by liver transplant
- Heterozygotes treated using drugs (statins) which reduce blood cholesterol (via inhibition of HMG-CoA reductase) which in turn up-regulates LDL receptors

The body contains different adipose tissue

- White adipose tissue (predominant)
  - Storage of excess calories as TAGs which can be used as fuel (via beta oxidation) to produce ATP (fuel reserve)
  - Prevention of toxic amounts of excess nutrients in non-adipose tissues
- Brown adipose tissue
  - Storage of TAGs, which are used as fuel (via beta oxidation)
  - Maintain core body temperature in response to cold (thermogenesis)

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Page 66 of 105

Revision

- Lipoproteins are particles of apolipoproteins and lipids
- 4 types of lipoproteins
  - Chylomicrons
  - LDL
  - VLDL
  - HDL
- Function of apolipoproteins → Solubilise lipids, cell targeting, enzyme activation
- Excess of LDL is associated with CV disease
- HDL removes excess cholesterol
- Receptor mediated endocytosis is the process by which LDLs are taken up by cells
- Drugs used to reduce blood cholesterol are known as statins
- Two main types of adipose tissue
  - White adipose tissue → Stores TAGs for beta oxidation → ATP
  - Brown adipose tissue → Thermogenesis (regulate body temperature)

Lipid and FA degradation

- TAGs
  - Glycerol backbone
  - 3 FA chains (Acyl chains)

Formation of ketone bodies from Acetyl-CoA

- Fatty acid derived acetyl CoA enters either the citric acid cycle or forms ketone bodies
- Ketone bodies → Acetoacetate, D-beta-hydroxybutyrate, acetone
- Acetoacetate and D-beta-hydroxybutyrate are used as an energy source by tissues under normal conditions or during starvation
- Ketone body production is low in health, well nourished individuals
- Ketone body production increases during starvation or in diabetes mellitus
- Ketone body production occurs mainly in the liver due to high levels of HMG-CoA synthase
- D-Beta-hydrobutyrate and acetoacetate become a source of acetyl CoA in extra hepatic tissues

Ketone body formation and export from the liver

- FA → Acetyl CoA (via beta oxidation)
- Some acetyl CoA → Ketone bodies
- Acetoacetate and D-beta-hydroxybutyrate exported as energy source for heart, skeletal muscle, kidney, brain
- Starvation/diabetes → Depletion of TCA intermediates (cannot function)
- Increase in ketone body formation → High blood and urine ketone body levels (ketosis) leads to acidosis, coma and death

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Page 71 of 105

Revision

- Beta oxidation of unsaturated FA requires additional steps involving isomerases and reductases
- Complete beta oxidation of odd chain fatty acids requires three additional steps
- The final product arising from the complete beta-oxidation of unsaturated FA is succinyl coA and the vitamin cofactor involved is vitamin B12
- Acetone, acetoacetate and D-beta-hydroxybutyrate are types of Ketone bodies
- Ketone body production occurs mainly in the liver due to high levels of HMG-CoA synthase
- Two health conditions associated with increased ketone body formation is starvation and diabetes mellitus
- Increase ketone body formation during starvation/diabetes because increased gluconeogenesis → Depletes TCA cycle intermediates → Prevent FA derived acetyl CoA from TCA cycle entry

TAGs

- Form main dietary lipid and storage lipid
- Glycerol backbone + 3FA chains

Fatty acid degradation

- TAGs → Glycerol and FA (in response to hormones → HSL)
- Glycerol → Gluconeogenesis/glycolysis

- Polar molecule

Cholesterol synthesis
- Acetyl CoA → Mevalonate → Isoprene → Squalene → Cholesterol
- HMG CoA synthase (Ketone body formation; acts on acetyl CoA to produce B-hydroxy which forms ketones)
- HMG CoA reductase (statins)

HMG-CoA reductase is the essential control point in cholesterol synthesis
- HMG-CoA also in ketone body formation
- HMG-CoA reductase is the target of cholesterol lowing compounds (drugs) called statins (eg lovastatin)

Cholesterol and related sterol synthesis
- From squalene other sterols are synthesised (stigmasterol and ergosterol)
- Squalene may act as an anti-oxidant or anti-cancer agent by increasing immunity

Cholesterol has several fates
- Bile acids (Used to solubilise TAGs in the gut so they can be digested by pancreatic lipases)
- Hydroxysterols (Roles in neuronal function)
- Cholesteryl ester (cholesterol + FA; useful way of transporting cholesterol around the body)
- Steroid hormones (pregnenolone)

Cholesterol and other lipids are carried on plasma lipoproteins
- Cholesteryl esters can be transported within lipoproteins

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Page 79 of 105

Bile salts originate from cholesterol
- Bile acids are derived from cholesterol in the liver
- Bile salts are comprised of bile acids (such as ionised cholic acid)
- Bile salts emulsify fats in the intestine, causing their digestion and absorption

Steroid hormones
- Sterol derivatives
- Lack alkyl chain attached to fourth (D) ring
- More polar than cholesterol which allows them to travel through the bloodstream on protein carriers
- Bind to highly specific receptors to induce changes in gene expression and metabolism (work through both cell surface and nuclear receptors)
- Give rise to
    - Sex hormones (testosterone, estradiol)
    - Hormones which regulate metabolism or salt secretion (cortisol, aldosterone)

Many energy carriers are derived from B group vitamins

- B2 (riboflavin) → FAD
- B3 (Niacin) → NADH, NADPH
- B5 (pantothenic acid) → Coenzyme A

Vitamin A

- Derived from beta carotene, which is formed from isoprene subunits
- Functions
  - Visual pigment in the vertebrate eye
  - Regulates gene expression in epithelial cells
- Deficiency results in
  - Night blindness
  - Cornea damage
  - Respiratory tract damage
  - GI damage

Vitamin A metabolism

- Beta carotene is cleaved → Vitamin A (retinol) → 11-cis-retinal
- 11-cis retinal (beta carotene derivative) may bind with opsin to form rhodopsin, a light sensitive receptor (responds to light)
- Visible light converts 11-cis-retinal to all-trans-retinal (a neuronal signal to the brain)
- 11-cis-retinal contains retinoic acid, a hormonal signal to epithelial cells

11-cis-retinal binds with opsin to form rhodopsin

- Rhodopsin is present in the rod/cone cells of the retina
- 11-cis-retinal is a light sensing pigment (chromophore)
- 11-cis-retinal covalently binds opsin to form rhodopsin
- 11-cis retinal converts to all-trans-retinal with UV light
- Rhodopsin undergoes a shape change sending a signal

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Page 81 of 105

Vitamin D synthesis

- 7-dehydrocholesterol, formed from cholesterol, is converted to biologically inactive vitamin D3 in the skin by sunlight (Via UV light)
- Vitamin D3 is converted to biologically active 1-alpha-25-dihydroxyvitamin D3 in the liver then kidney
- 7 dehydrocholesterol → UV light (2 step process in the skin) → Cholecalciferol (Vitamin D3) → 2 step process (1 in the liver, 1 in the kidney) → 1alpha,25-Dihydroxyvitamin D3 (calcitriol)

Vitamin D and bone metabolism

- 1,25-dihydroxyvitamin D3 regulates calcium and phosphate metabolism to promote bone metabolism
- 1,25-dihydroxyvitamin D3 deficiency impairs bone mineralisation leading to bone disease (rickets and osteomalacia)

Vitamin D deficiency

- Due to poor dietary intake and/or reduced sun exposure

- RNA/DNA when nucleic acid
- Ribonucleotides have the ribose sugar, deoxyribonucleotides if they do not have the sugar

Pyrimidine nomenclature

- Cytosine
- Nucleoside (sugar + base) → Cytidine
- Nucleotide → Cytidylate

Roles of nucleotides

- Transfer of energy (ATP, GTP)
- Regulation of cellular metabolism (AMP levels)
- Components of major coenzymes (NAD+, FAD)
- Storage and transfer of genetic information
    - Activated precursors of DNA and RNA
- Signal transduction in cells, second messengers
    - Cyclic AMP, cyclic GMP mediates hormonal actions
- Extracellular signalling molecules
    - Extracellular ligands for receptors
    - Adenosine is a neurotransmitter

Transfer of energy (ATP)

- ATP provides energy for many reactions
    - Synthesis of macromolecules
    - Active transport of molecules and ions across membranes
    - Contraction of muscle cells
- Works by coupling an unfavourable reaction to energy release from ATP hydrolysis
- The donation of energy from ATP generally involves the covalent participation of ATP in the reaction that is to be driven
- Most cases of energy transfer from ATP involve group transfer (phosphate groups moving)
- The covalent participation of ATP can be to form an activated intermediate
    - Eg production of glutamine by ATP dependent glutamine synthetase
    - Glutamate + ATP → Intermediate → Glutamine

Regulation of cellular metabolism (AMP)

- AMP concentration is a sensitive indicator of a cell's energetic state
    - When ATP is broken down, [AMP] increases
    - Indicates energy use and that energy needs to be generated
- AMP activated protein kinase (AMP kinase)
    - Most important mediator of regulation by AMP
    - Responds to increased AMP concentrations (decreased ATP/AMP ratio) in response to decreased intake of nutrients by cell or increased use (exercise)
    - Activates or inhibits a range of metabolic processes

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Page 83 of 105

    - Ring stabilises it
- Two forms of chlorophyll depending on its sidechain, absorb light in slightly different regions
    - Chlorophyll a (more common)
    - Chlorophyll b

Why are leaves green?

- Chlorophyll absorbs light in the blue and red regions of visible light
- Light in the green region is reflected

Accessory pigments

- Secondary light absorbing pigments are called carotenoids (Important so you can absorb as much light as possible)
- The two most important are
    - Beta carotene (red-orange)
    - Lutein (yellow)
- These pigments absorb light at wavelengths not absorbed by chlorophyll and thus serve as supplementary light receptors
- Different proportions of these pigments give plant species their characteristic colour

Light harvesting complexes (LHCs)

- Specific proteins fix the position of light harvesting pigment molecules into membrane (carotenoids and chlorophyll)
- Embedded in the thylakoid membrane

Light harvesting (Photosystems I and II)

- The light absorbing pigments are arranged in arrays called photosystems that are embedded in the thylakoid membrane
- Excitation energy (exciton) from absorbed photons is transferred between antenna chlorophylls to a reaction centre
- Excited state transfers randomly from one chlorophyll to another til it reaches reaction sensor

Exciton and electron transfer

- All pigment molecules can absorb photons but only specialised chlorophyll molecules associated with the photochemical reaction centre can transduce light into chemical energy (the others pass it on)
- Photon of visible light used to push electron to outer orbital
- Antenna chlorophylls (bound to protein), carotenoids and other accessory pigments absorb light energy, transferring it between molecules until it reaches the reaction centre
- A photochemical reaction occurs in the reaction centre that converts the energy of a photon into a separation of charge, initiating electron flow (starts electron transport chain)
- Photon pushes electron to outer orbital which makes it a good electron donor (this is how it can pass it on to electron acceptor which is then reduced)

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Page 90 of 105