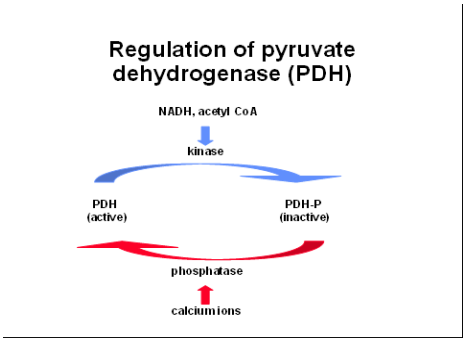
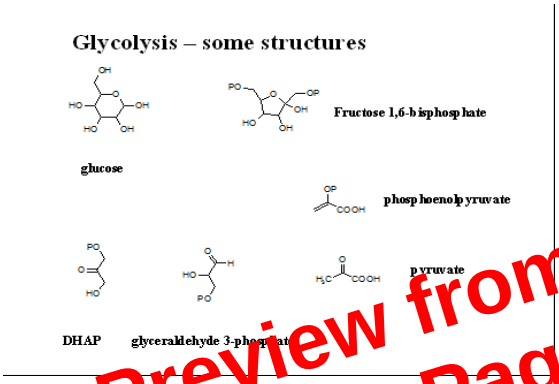
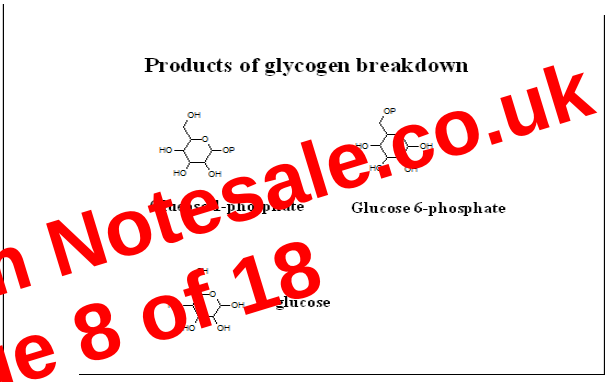
level of F26P2, Switches off glycolysis If blood glucose low then glycolysis switched off.
  - F6P + ATP --> F26P2 + ADP - phosphofructokinase 2
  - Liver enzyme inhibited by cAMP-dependent phosphorylation. Heart muscle enzyme stimulated by cAMP-dependent phosphorylation - Adrenaline stimulates F26P2 production, Stimulates glycolysis, Co-ordinates glycogen breakdown and glycolysis.
- Hexokinase - Inhibited by G6P, If PFK inhibited then G6P will rise and feedback, Prevents unnecessary conversion of glucose to G6P. Isoenzymes - Liver – isoenzyme IV (glucokinase, high K_m) – not inhibited by G6P.
- Pyruvate kinase - Allosteric, ATP inhibits - Signals abundance of energy, F1,6P_2 stimulates - Keeps glycolysis going (feed forward activation). Reversible covalent modification (liver only) - Glucagon stimulates phosphorylation via cAMP leading to inhibition.
- Chronic control of glycolysis - insulin promotes synthesis of some glycolytic enzymes, glucagon promotes synthesis of some gluconeogenic enzymes.
- Pyruvate dehydrogenase - Pyruvate + NAD + CoA/acetylCoA + NADH + CO_2. Entry in to TCA cycle, Effectively irreversible, Commits pyruvate, Multiple control. Regulated by reversible covalent modification - cAMP independent.

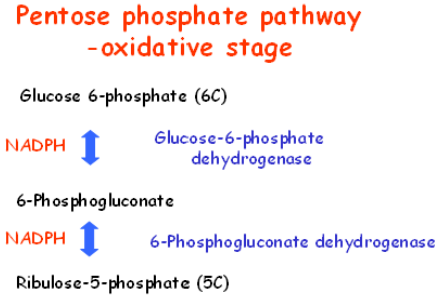


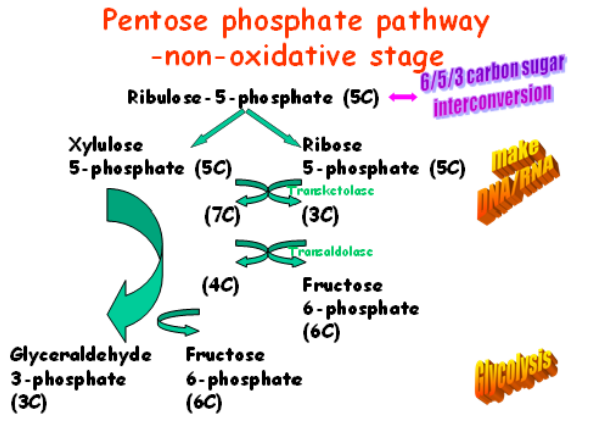




Week 6 - Pentose pathway/Lipoproteins

- Pentose phosphate pathway - synthesis of NADPH, Sugars other than hexoses, e.g. Pentose for nucleic acid synthesis. Inter-conversion of 6/5/3 carbon sugars. Active in adipose tissue - fatty acid synthesis. Control by allosteric inhibition of G-6-P dehydrogenase with NADPH. G6PDH deficiency causes haemolytic anaemia - in red blood cells and harms metabolism causing lysis.
- Oxidative stage - makes 2 molecules of NADPH, generates ribulose 5-phosphate.
- Non-oxidative stage - 2 reaction chains to make different lengths sugars. Ribose-5-phosphate used to make DNA/RNA. Glyceraldehyde-3-phophate used in glycolysis.

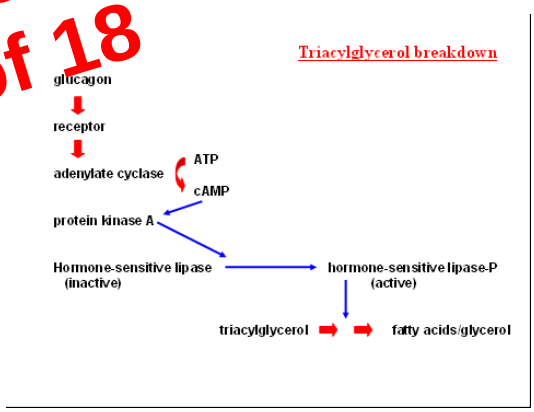




- Cholesterol transport - cholesterol not readily soluble in plasma - transported in lipoproteins.
- Lipoproteins - Main lipids - Chylomicrons - e.g. Dietary triacylglycerol. VDLD - e.g. endogenous triacylglycerol. IDL/LDL - e.g. Cholesteryl ester. HDL - phospholipid/Cholesteryl ester. Named on basis of density, Protein is denser than lipid, e.g. chylomicrons are 2% protein/98% lipid by weight and have density of <0.95 g/ml. HDL is 55% protein/45% lipid and has density 1.063-1.21 g/ml
- Lipoprotein lipase - Enzyme bound to lumenal surface of endothelial cells in capillaries mainly in skeletal muscle, adipose tissue and heart. Hydrolyses triagylycerols to two fatty acids and one monoacylglycerol, Products taken up by skeletal muscle or heart for energy production by β-oxidation or adipose tissue for conversion to triacylglycerol for energy storage.
- Apo B-100 - attaches LDL to LDL receptors on cells - allows cholesterol delivery to cells. Important for regulating plasma LDL and plasma cholesterol levels. LDL receptor - mediated endocytosis - binds to coated pit then moved inside by a vesicle.
- Cholesterol excretion - converted to bile acids in the liver. Rate limiting enzyme is cholesterol 7α-hydroxylase. Bile acids are excreted into the bile and then into small intestine and faeces, Solubilise dietary lipids.
- Atherosclerosis - Deposition of cholesterol (mainly cholesteryl ester) in arteries. Eventual block due to thrombosis, High levels of LDL a risk factor, Uptake of modified LDL by macrophages, Cholesterol loading (foam cells) in arteries. Risk factors - high saturated fat diet. Deficiency in LDL receptors - leads to reduced rate of LDL clearance so high LDL numbers in blood.

Week 7 - Fatty acid breakdown and synthesis.

- Fatty acid breakdown - Fat as a major fuel store. Adipose tissue in mammals as fat globules. Highly concentrated, anhydrous, highly reduced, higher energy per gram than carbohydrate.
- Triacylglycerol - glycerol molecule esterified with 3 fatty acids. Saturated, monounsaturated and polyunsaturated fatty acids. Breakdown - Yields fatty acids and glycerol. Hormone-sensitive lipase (triacylglycerol lipase), Stimulated by hormones e.g glucagon, adrenaline. Fatty acids used as fuel, Glycerol used in glycolysis/gluconeogenesis.



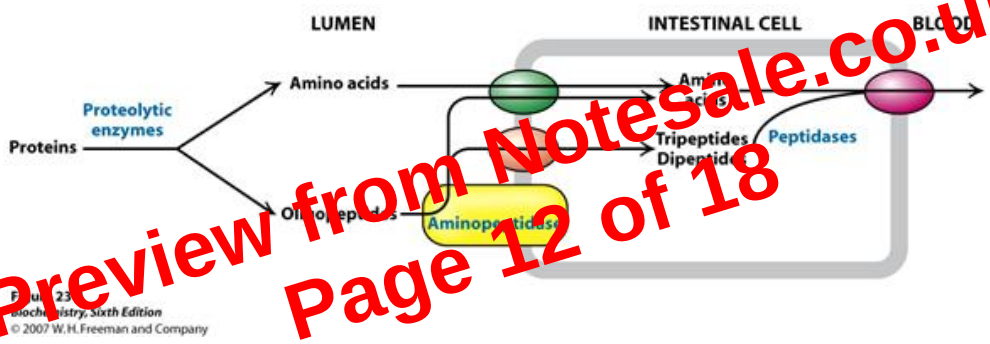
- Fatty acids bind to albumin - Fatty acids are insoluble in water. Therefore bind to albumin in plasma for circulation around the body, Released from adipose tissue and circulate to skeletal muscle or heart for b-oxidation.
- Fatty acid oxidation - mitochondiral b-oxidation. 2 carbon units removed in each cycle.
- Fatty acid oxidation – entry in to mitochondrion. Fatty acyl CoA in cytosol. Converted to acyl carnitine by carnitine acyltransferase. Cross mitochondrial membrane as fatty acyl carnitine. Reconvert to fatty acyl CoA in mitochondrion. Each round yields acetyl CoA, NADH, $FADH_2$. Complete oxidation of palmitoyl CoA yields 129 ATP ultimately. Fixes ~40% of energy. Odd numbered fatty acids (found in small amounts in vegetables) yield acetyl CoA and one molecule of propionyl CoA - Propionyl CoA is converted to succinyl CoA and enters citric acid cycle. Unsaturated fatty acids - Move double bonds from one position to another on the fatty acid, Remove double bonds by making them saturated using NADPH if necessary. Control by supply of fatty acids - Rate of triacylglycerol breakdown. Inhibited by malonyl CoA (intermediate in fatty acid synthesis) when fuel molecules are abundant, Inhibits acyl carnitine production.

activated protein kinase, when energy stores are low, AMP is high. Enzyme stimulated by insulin, inhibited by glucagon.

- Elongation of palmitic acid - Elongation system on cytosolic face of endoplasmic reticulum. Enzymes use malonyl CoA to add two carbon units to the carboxyl ends of fatty acids.
- Desaturation of fatty acids - fatty acyl CoA desaturases in endoplasmic reticulum.
- Essential fatty acids - Mammals can add double bonds to carbon atoms up to, but not beyond, C9 – C10 in fatty acid chain. Therefore essential fatty acids linoleic acid (C18:2) and linolenic acid (C18:3) must come from diet.
- Triacylglycerol synthesis - Fatty acid availability, Glucose metabolism, Supplies glycerol units. Anabolic state - insulin high, adrenaline and glucagon low, Triacylglycerol breakdown low. Synthesis in adipose tissue and liver - No

Week 8 - Amino acid metabolism

- Dietary protein - proteins have to be digested in the stomach and intestine to provide a steady supply of amino acids for cellular needs.
- Protein turnover - Many cellular proteins are constantly degraded and resynthesized in response to changing needs. Balance of synthesis and breakdown, varies for different proteins, necessary for normal cellular and physiological processes. Needed to remove damaged proteins. Tightly regulated - Ubiquitin tags protein for degradation, ubiquitinated proteins are broken down into amino acids



- Protein degradation occur in starvation - to provide cellular fuels, diabetes - to produce more glucose and trauma - shock phase causes hypermetabolic flow, increases heat production and metabolic expenditure. Fat mobilisation, muscle protein degradation, general increase in substrate/fuel supply for survival and repair.
- Essential amino acids - must be supplied in diet. Excess amino acids cannot be stored, protein breakdown to supply these if not in diet.
- Regulation of protein breakdown - control by hormones - insulin suppresses breakdown, insulin promotes synthesis, insulin promotes amino acid uptake in to cells, insulin low during starvation - promotes protein breakdown mediated by proteases.
- Amino acids as metabolic precursors - protein synthesis, as cellular fuels, as precursors for biosynthesis; serine needed for lipid biosynthesis, glycine needed for porphyrin synthesis, arginine needed to make nitric oxide.
- Catabolism of amino acids - excess cannot be stored and have to be degraded. Degradation starts with removal of amino group.