The Liver
General Metabolism

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Outline of Liver Lectures

- General Metabolism
- Biotransformations
- Lipoprotein Metabolism

Aims & Objectives

On completion of this lecture you should:

1. Have an understanding of the basic structure of the liver and how this relates to its physiological & biochemical function
2. Be aware of the major metabolic pathways occurring in hepatic tissues
3. Be able to describe the liver's role in glucose homeostasis and direct and reverse reactions

History

Aristotle, 350 B.C.E

"..liver is not only useful, but a necessary and vital part in all animals that have blood…"

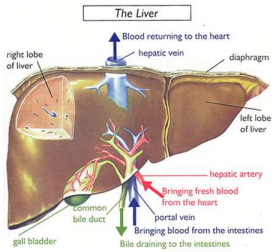
Galen, 200 A.D.

"Now, why is the stomach surrounded by the liver? Is it in order that the liver may warm it and it may in turn warm the food? This is indeed the very reason why it is closely clasped by the lobes of the liver, as if by fingers."

How many lobes?

The Liver

- Largest internal organ of the human body with highest temperature
- Segmented structure comprising four main cell types
  - Hepatocytes (parenchymal cells)
  - Endothelial cells (also Kupffer cells)
  - Epithelial cells
  - Mesenchymal cells
- Dual blood supply (hepatic artery & portal vein)
- Essentially a large exocrine gland



Functions of the Liver

Carbohydrate (CH_2O) Metabolism
- Glycolysis
- Formation and storage of glycogen
- Conversion of galactose & fructose into glucose
- Gluconeogenesis

Fat Metabolism
- Oxidation of fatty acids for energy
- Synthesis of cholesterol, phospholipids & most lipoproteins
- Synthesis of fat from proteins and CH_2O

Protein Metabolism
- Transamination of amino acids
- Interconversion of proteins and amino acids
- Formation of urea
- Synthesis of plasma proteins (albumin)

Vitamins
- Storage of vitamin A, E, D and B_{12}

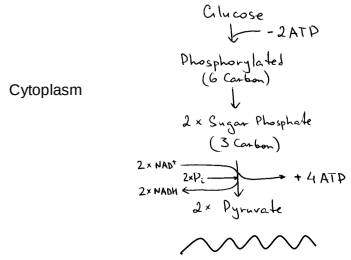
Coagulation Factors
- Synthesis of fibrinogen, prothrombin and Factor VII

Hormons production
- Angiotensinogen, insulin-like growth factor 1 (IGF-1), thrombopoietin

Metall ions storage
- Hepatocytes capture iron (apoferritin) and store it as ferritin
- Copper

Removal of substances in bile
- Drugs (*e.g.* penicillin, paracetamol)
- Hormones (*e.g.* estrogen)
- Bilirubin

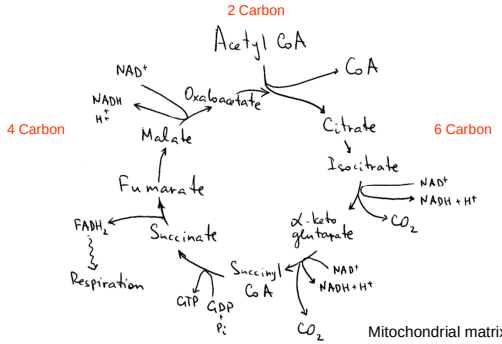
Carbohydrate Metabolism



Cytoplasm

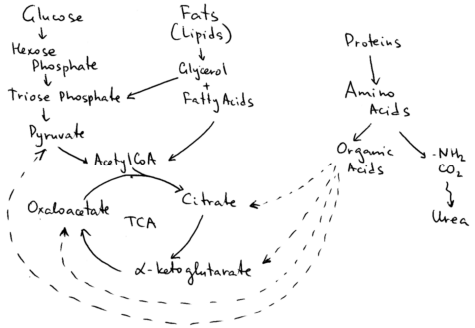
Mitochondrial matrix

Krebs cycle (TCA cycle)



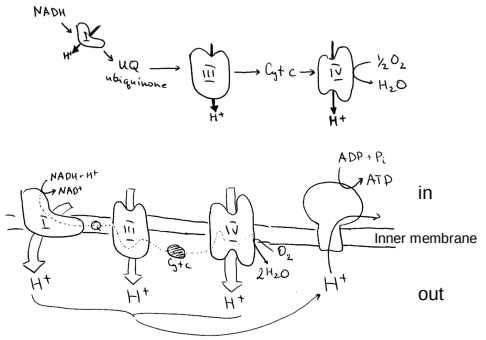
Mitochondrial matrix

Metabolic network

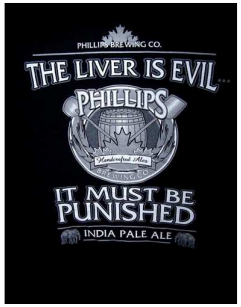


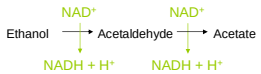
Unification of substrates

Respiration and ATP synthesis



Most Important Function of the Liver . . .





Two systems to metabolise ethanol:

Alcohol dehydrogenase (ADH) (i) and microsomal cytochrome P_{450} (ii)

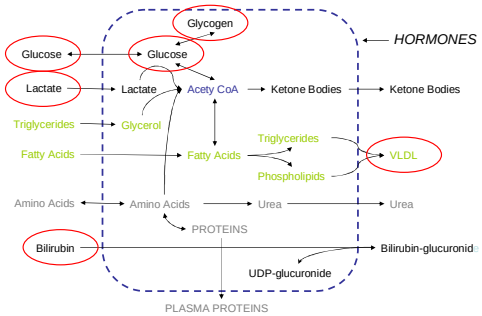
In healthy person most of ethanol is metabolised by ADH with NADH production

Small proportion of ethanol is metabolised by the microsomal Cytochrome P_{450} system with oxygen consumption and ROS production.

NADH inhibits gluconeogenesis and β-oxidation of fatty acids.

Hence, excessive alcohol consumption leads to accumulation of fatty acids ('fatty liver')

Liver's Role in Metabolism



Liver's Role in Metabolism

Central metabolic "clearinghouse"=processing unit

Blood glucose buffer

- Metabolism other hexoses
- Gluconeogenesis
- Glycogen synthesis/breakdown and storage

Production ketone bodies

Lipogenesis, the production of triglycerides (fats)

Cholesterol synthesis

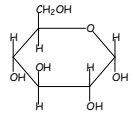
Haemoglobin breakdown → bile production

Detoxification of xenobiotics

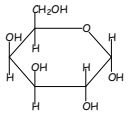
Plasma protein secretion

Metabolic flexibility

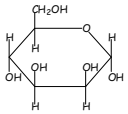
Common hexoses



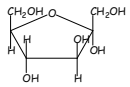
a-D-Glucose



a-D-Galactose



a-D-Mannose



a-D-Fructose

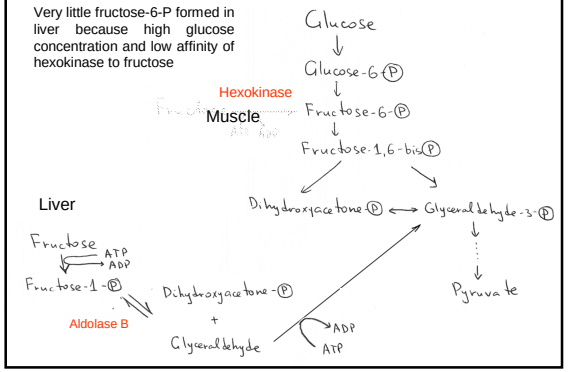
+di and oligosacchrides

Common hexoses

Sugar	Source	Importance	Clinical Significance
D-Glucose	Fruit juices. Hydrolysis of starch, cane sugar, maltose, and lactose.	The "sugar" of the body. The sugar carried by the blood, and the principal one used by the tissues.	Present in the urine (glycosuria) in diabetes mellitus owing to raised blood glucose (hyperglycemia).
D-Fructose	Fruit juices. Honey. Hydrolysis of cane sugar and of inulin (from the Jerusalem artichoke).	Can be changed to glucose in the liver and so used in the body.	Hereditary fructose intolerance leads to fructose accumulation and hypoglycemia.
D-Galactose	Hydrolysis of lactose.	Can be changed to glucose in the liver and metabolized. Synthesized in the mammary gland to make the lactose of milk. A constituent of glycolipids and glycoproteins.	Failure to metabolize leads to galactosemia and cataract.
D-Mannose	Hydrolysis of plant mannans and gums.	A constituent of many glycoproteins.	

Metabolism of fructose

Very little fructose-6-P formed in liver because high glucose concentration and low affinity of hexokinase to fructose



Metabolism of fructose

Fructose ~30-60% of carbohydrate intake in mammals.

Fructose intolerance – deficiency in liver aldolase B

Fructose – Fructose-1-P accumulation with ATP usage

Fructose + ATP → Fructose-1-P + ADP
ADP + P_i → ATP *(in any ATP-producing reaction, e.g OXPHOS)*

Fructose + P_i → Fructose-1-P + ADP

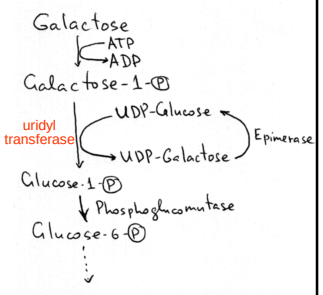
P_i is tied up to fructose ⇒ Depletion of P_i ⇒ impossible to make ATP from ADP

Used before for parenteral nutrition (it was believed that utilisation is insulin-independent). However, delivery of large amounts of fructose intravenously resulted in severe liver damage.

Metabolism of galactose

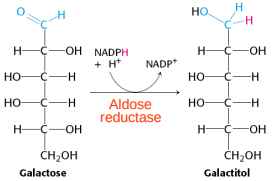
Galactosemia

- Classical galactosemia affects 1 in every 55,000 newborns
- Can be caused by the enzyme deficiency at each step
- Most severe cases due to deficiency of the enzyme galactose 1-phosphate uridylytransferase
- Unmetabolised galactose is reduced to galactitol (cataract formation & CNS damage)
- Accumulation of galactose 1-P leads to liver damage



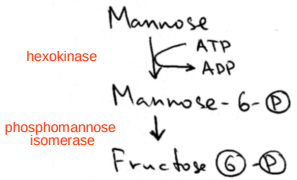
Galactosemia

Cataract formation



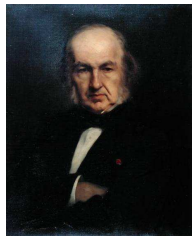
Treatable by diet, however, in the most galactosemic patients this treatment does not prevent development of late-onset complications: mental retardation, ovarian failure and neurologic disturbances (nerve tissue glycolipids)

Mannose metabolism



95% of mannose is excreted within hours after consumption
Part of glycoproteins

Claude Bernard & glucose/liver



Measurements of glucose blood level in fed and fasting animals

He was surprised to find glucose in blood samples - from animals and man - who were eating a diet completely free of carbohydrates. Moreover, even if they had been fasting for several days. Could this mean that some glucose was being synthesized in the body itself?

Not only storage but synthesis!

Gluconeogenesis

Why would we need to synthesize glucose?

Glucose is primary fuel for brain and red blood cells.

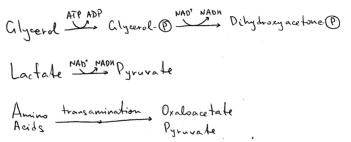
Brain consumes ~120g glucose/day (out of 160g of daily intake)

Amount readily available is ~20g

Stored in form of glycogen is ~180g - enough for 1 day

What happens on a second day?

Glucose can be synthesised from lactate, amino acids and glycerol



Gluconeogenesis. Precursors.

Lactate, Amino Acids and Glycerol

- Lactate returns to the liver, is re-oxidised to pyruvate and fed into gluconeogenesis. The combination of glycolysis in peripheral tissues with hepatic gluconeogenesis is referred to as the Cori cycle
- Some amino acids are directly converted to glucose (glucogenic amino acids); others are first converted to ketone bodies (ketogenic amino acids)
- Glycerol is taken-up by the liver and phosphorylated by glycerol kinase and dehydrogenated to dihydroxyacetone phosphate

However!!! Fatty acids with even C-atoms CANNOT be glucose precursors. Acetyl-CoA cannot be converted into pyruvate or oxaloacetate in animals.

Who are these people?!?!

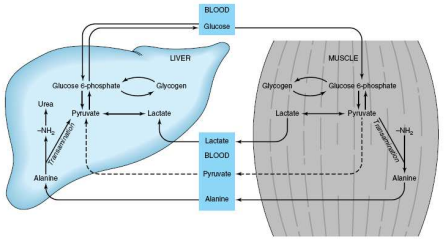
Cori and alanine cycle

Cori cycle = glucose-lactate cycle

Alanine cycle = glucose-alanine cycle (gluconeogenesis and urea formation)

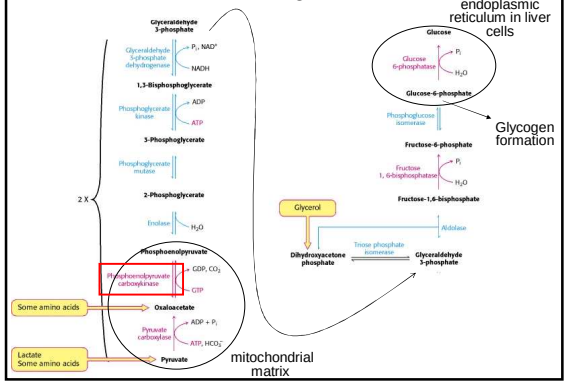
Lactate – Muscle and red blood cells

Alanine - muscle in starvation

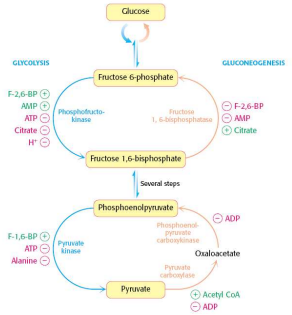


Different isoforms of enzymes catalyse forward and reverse reactions in different tissues

Gluconeogenesis

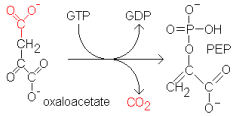


Glycolysis and gluconeogenesis regulation



Direct and reverse reaction – futile cycle - flux control

Super mouse



Phosphoenolpyruvate carboxykinase

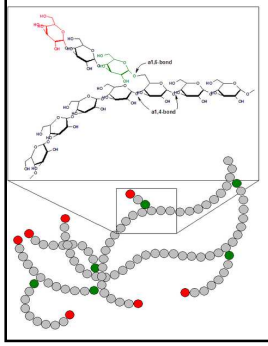
Supermice have up to 100 times the concentration of the enzyme in muscles in its muscles compared with WT mice.

Eat twice as much as WT, live longer, reproductively active and more aggressive

Hepatic Glycolysis

- The liver has a very specialised role in glucose metabolism
- If blood glucose is high, the liver removes a large fraction for storage as glycogen or fat
- If blood glucose is low, the liver only removes a small amount of glucose
- This mechanism is regulated in two ways
  - *Hepatic glucose uptake:* the hepatic glucose transporter (GLUT 2) has a higher K_m ∴ reduced rate of transport at low [glucose]
  - *Phosphorylation of glucose to glucose 6-P:* the liver has a separate enzyme (glucokinase) which performs the same reaction as hexokinase, but it has a higher K_m ∴ reduced rate of phosphorylation at low [glucose]

Glucose and glycogen

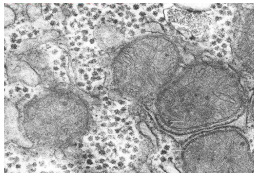


Glycogen - branched polymer of glucose, readily mobilized storage of glucose

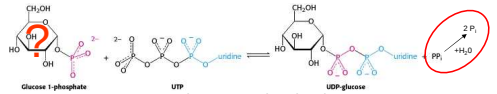
α-1,4-glycosidic and α-1,6-glycosidic linkage

10% of liver weight ~180g (1-2% in muscle)

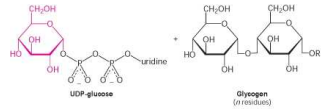
Molecules up to ~ 2×10^7 Da in glycogen granules in liver ~200-400Å



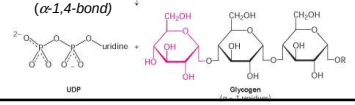
Glycogenesis



UDP-glucose pyrophosphorylase



Glycogen synthase
(α-1,4-bond)



Glycogenesis

Primer is required for synthesis – chain is attached to special protein glycogenin. It is two 37kDa subunit protein each subunit can catalyse addition of 8 units of glucose to via –OH group of specific tyrosine on its counterpartner.

However, branching (α-1,6-bond formation) is required for increase of solubility and accessibility (synthesis/degradation rate). Special, very specific branching enzyme α-1,4-glucan-6-glycosyltransferase catalyses that reaction.

$$\text{Glucose 6-phosphate} \longrightarrow \text{glucose 1-phosphate} \quad (1)$$

$$\text{Glucose 1-phosphate} + \text{UTP} \longrightarrow \text{UDP-glucose} + PP_i \quad (2)$$

$$PP_i + H_2O \longrightarrow 2\,P_i \quad (3)$$

$$\text{UDP-glucose} + \text{glycogen}_n \longrightarrow \text{glycogen}_{n+1} + \text{UDP} \quad (4)$$

$$\text{UDP} + \text{ATP} \longrightarrow \text{UTP} + \text{ADP} \quad (5)$$

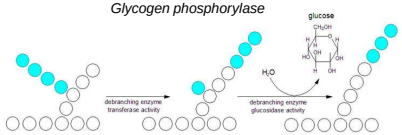
$$\text{Sum: Glucose 6-phosphate} + \text{ATP} + \text{glycogen}_n + H_2O \longrightarrow \text{glycogen}_{n+1} + \text{ADP} + 2\,P_i$$

Glycogen degradation

I $\quad \underset{(n\text{ residues})}{\text{Glycogen}} + P_i \rightleftharpoons \text{glucose 1-phosphate} + \underset{(n-1\text{ residues})}{\text{glycogen}}$

Glycogen phosphorylase

Ia



Transferase & α-1,6-glucosidase= single 160kDa enzyme
(two activities)

II $\quad$ glucose 1-phosphate ⟶ Glucose 6-phosphate

Phosphoglucomutase

III $\quad \text{Glucose 6-phosphate} + H_2O \longrightarrow \text{glucose} + P_i$ *liver specific enzyme located in ER*

Glucose 6-phosphatase

Glycogen degradation/synthesis

Synthesis: $\text{Glycogen}_n + \text{UDP-glucose} \longrightarrow \text{glycogen}_{n+1} + \text{UDP}$

Degradation: $\text{Glycogen}_{n+1} + P_i \longrightarrow \text{glycogen}_n + \text{glucose 1-phosphate}$

Glycogen phosphorylase

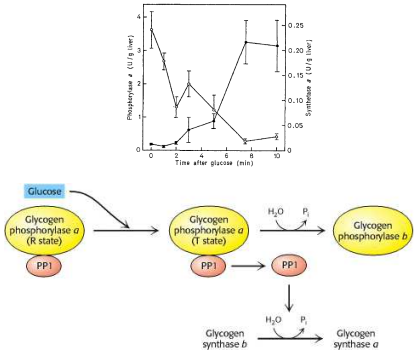
– Covalent - Phosphorylation by Protein Kinase (PKA-dependent)
  - active (a) form is phosphorylated
  - inactive (b) form is dephosphorylated
– Allosteric – Phosphorylase activator – AMP
– Allosteric – Phosphorylase inhibitor - ATP, G6P and glucose

Glycogen synthase

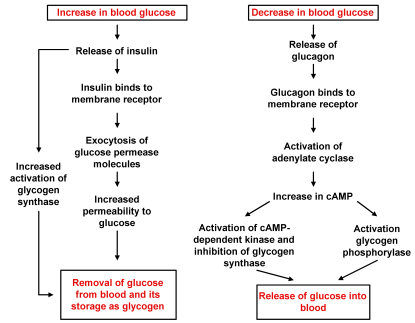
– Covalent - phosphorylated at C and N terminals increases net charge from -13 to -31
  - active (a) form is dephosphorylated
  - inactive (b) form is phosphorylated

– Allosteric – Synthase activator – Glucose

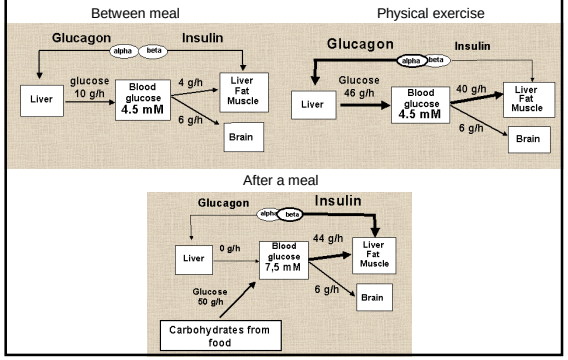
Glycogen phosphorylase *vs.* synthase



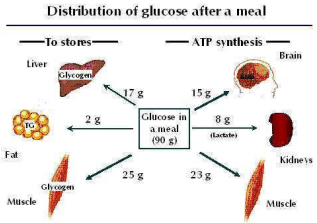
Blood glucose



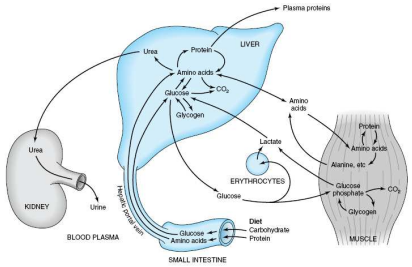
Blood glucose



Blood glucose



Liver's Role in Metabolism



Summary

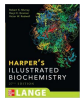
- The liver plays a key role in mammalian metabolism – the laboratory of the human body
- The liver has an especially important role in glucose homeostasis = glucose synthesis and glycogen synthesis/degradation/storage
- Direct and reverse reactions are directed via different pathways
- Disruption of the liver's function has serious consequences for normal physiology

Text books

Biochemistry (Berg, Tymoczko & Stryer)

16.1 – 16.4; 17.1 – 17.3; 21.1; 21.2; 21.4; 21.5

22.3.5 – 22.3.7; 23.3; 23.6; Chapter 30



Harper's Illustrated Biochemistry (LANGE Basic Science), Robert K. Murray, D. Granner, P. Mayes, V.Rodwell

Also Level 1 Biochemistry lectures notes ('Energy Metabolism', Dr Timson)

Good biochemistry lecture notes and videos from MIT are available online :
http://ocw.mit.edu/OcwWeb/Biology/7-014Spring-2005/VideoLectures/index.htm

Further Reading II

Proteolytic and lipolytic responses to starvation
P. F. Finn & J. F. Dice
Nutrition (2006) 22: 830 – 844
Sections of relevance are: lipolytic responses to starvation, breakdown of TAG, movement of acyl-CoA into the mitochondria, production of ketone bodies, concluding remarks

Regulation of hepatic glucose production and the role of gluconeogenesis in humans: is the rate of gluconeogenesis constant?
F. Q. Nuttall, A. Ngo & M. G. Gannon
Diabetes/Metabolism Research & Reviews (2008) 24: 438 – 458
Sections of relevance are: introduction, regulation of glycogenolysis, regulation of gluconeogenesis

Pathways and control of ketone body metabolism: on the fringe of lipid biochemistry
T. Fukao, G.D. Lopaschuk & G.A. Mitchell
Prostaglandins, Leukotrienes and Essential Fatty Acids (2004) 70: 243 - 251
Entire paper provides a good overview of ketone body metabolism

Triglyceride Metabolism I

Digestion of triglycerides (TG) occurs in four stages

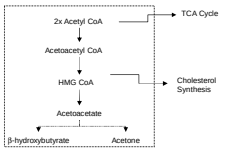
- *Action of bile acids:* these detergents solubilise TG, rendering it accessible for enzymic cleavage
- *Action of lipase:* this pancreatic enzyme hydrolyses TG into 2-monoacylglycerol plus 2x fatty acids (FA)
- *Secretion of chylomicrons:* 2-monoacylglycerol and FAs are re-esterified in intestinal epithelial cells and packaged as chylomicrons
- *Metabolism of TG:* lipoprotein lipase binds chylomicrons and cleaves TG. Cleavage products are either stored in adipose (as TG) or metabolised by oxidative degradation

Triglyceride Metabolism II

- FA are initially activated to fatty acyl CoA in cytosol. They are transported across the mitochondrial membrane *via*. the carnitine exchange cycle.
- Saturated FA are broken down by β-oxidation to produce acetyl CoA (→ TCA cycle → ATP)
- Unsaturated FA must undergo additional reactions before entering the β-oxidation pathway
- Oxidation of FA produces a high yield of ATP – for example, the complete oxidation of palmitate (C16:0) produces 129 ATPs
- The liver also converts FA into ketone bodies, which are exported into the circulation

Ketone Bodies

- Water-soluble forms of lipid-derived 'energy' produced by hepatocytes
- Formed from acetyl CoA (produced during β-oxidation)
- Acetoacetate is the major product of ketone body synthesis; some is reduced to β-hydroxybutyrate.
- Acetoacetate continually undergoes slow, spontaneous non-enzymic decarboxylation to acetone
- Formation of acetone is normally negiligible, except in
  - Diabetic ketoacidosis (DKA)
  - Infection



Utilisation of Ketone Bodies

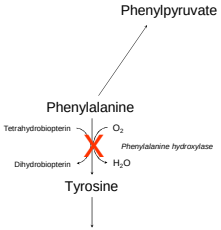
The brain, muscle and other tissues use ketone bodies for ATP production. Initially, β-hydroxybutyrate is converted to acetoacetate (extra-hepatically), which is then converted to acetoacetyl CoA. The enzyme thiolase cleaves acetoacetyl CoA to acetyl CoA → TCA cycle.

Amino Acid Metabolism

- The α-amino group is removed by transamination
- Transaminases catalyse the reaction:
- α-amino acid + α-ketoglutarate ⇔ α-keto acid + glutamate
- Glutamate is degraded by glutamate dehydrogenase, releasing NH4+ (→ Urea Cycle)
- The carbon skeleton is converted to one or more metabolic intermediates, or for use as metabolic fuel
  - Amino acids which are degraded to pyruvate, α-ketoglutarate, succinyl CoA, fumarate and oxaloacetate are called 'glucogenic' (directly into gluconeogenesis)
  - Those degraded to acetyl CoA or acetoacetyl CoA are termed 'ketogenic' (produce ketone bodies)

Phenylketonuria (PKU)

- Phe is a hydrophobic, aromatic amino acid
- It is initially converted to Tyr by phenylalanine hydroxylase
- This reaction requires the coenzyme tetrahydrobiopterin
- The inborn error of metabolism phenylketonuria occurs from an inability to metabolise Phe
- The main form arises from a deficiency in pheylalanine hydroxylase
- Resulted in increased phenylalanine level in blood and mental retardation. Nobody knows why.



Metabolism of Vitamins

Example: Activation of Vitamin D

- Sunlight converts 7-dehydrocholesterol to cholecalciferol which is transported to the liver for conversion to calcidiol (pre-vitamin D_3)
- Calcidiol is transported to the kidneys for conversion to calcitriol (active vitamin D_3)
- Calcitriol stimulates increased intestinal absorption of calcium in conjunction with parathormone

Liver Dysfunction I

Liver Function Tests (LFTs)

Alanine aminotransferase (ALT)	Leaks from damaged hepatocytes into blood; rises dramatically in acute liver damage (*e.g.* hepatitis or paracetamol overdose)
Aspartate transaminase (AST)	Similar to ALT, but also present in RBC & muscle (∴ not liver specific); can use ALT-to-AST ratio
Alkaline phosphatase (ALP)	Produced by cells lining biliary ducts in liver (also bone and placenta); elevated ALP indicates bile duct obstruction
γ-Glutamyl transpeptidase (γ-GT)	Mainly produced by the liver; increased in alcohol toxicity (acute & chronic)
Total Bilirubin (TBil)	Increased in bile duct obstruction (e.g. gallstones, tumour) and cholestasis from drugs
Conjugated Bilirubin (CBil)	Increased in anaemia, hepatitis, cirrhosis, erythroblastosis fetalis If CBil is normal, but TBil is raised, then liver dysfunction is upstream of bilirubin excretion. If CBil is elevated, then bile duct obstruction is likley
Albumin	Not specific; levels decrease in liver dysfunction

Liver Dysfunction II

- Acute Liver Disease
  - Primary causes: infection or chemicals/drugs
    Example: acute viral hepatitis
    Symptoms: dark urine (hyperbilirubinaemia *c.f.* Liver II), hepatomegaly (enlarged liver due to edema), abnormal LFTs
  - Secondary causes: cardiovascular disease
    Example: heart failure
    Symptoms: increased serum bilirubin, abnormal LFTs
- Chronic Liver Disease
  - Example: alcoholic liver disease
  - Symptoms: hepatomegaly, fatty liver, jaundice, abnormal LFTs
- Genetic Hepatobiliary Disorders
  - Haemochromatosis (Fe storage); Wilson disease (Cu storage)

The Liver II: Biotransformation

Dr Alexander Galkin

Level 2 Mammalian Biochemistry

Aims & Objectives

This lecture will cover the following areas:

- Biotransformation of endogenous and exogenous compounds *via*. Phase I and Phase II systems
- Cytochrome P450 system and its role in detoxification
- The role of glucuronic acid in bilirubin metabolism
- The metabolism of cholesterol and its excretion as bile acids

Biotransformation I

What is Biotransformation

- Synonymous with detoxification
- Mammals acquire potentially dangerous compounds (xenobiotics) from their environment
  - Xenobiotics tend to be hydrophobic (they will accumulate in fat)
  - These must be made less harmful prior to excretion

Biotransformation II

How is Biotransformation Achieved

- Enzyme systems convert hazardous compounds to less hazardous products
- Wide variety of 'toxins' ⇒ Detoxification enzymes must have broad specificity

The Liver's Role in Biotransformation

- It's the largest internal organ
- First pass of substances absorbed in GI tract
- High concentration of enzyme systems required (mainly in hepatocytes' endoplasmic recticulum)

Overview of Enzyme Systems

Phase I Reactions

- Oxidoreduction and hydroxylation + deamination, dehalogenation, desulfuration
- Inactivation/activation (?) + producing a more polar compound (water soluble)

cytochrome P450 systems
monooxygenases

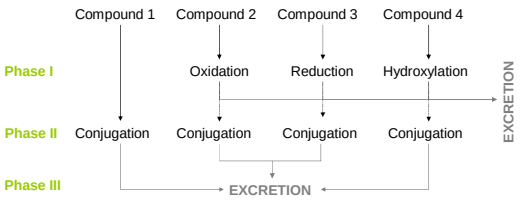
Phase II Reactions

- Conjugation or metylation
- Transfer a solubilising group to substrate - producing a more polar compound (water soluble)

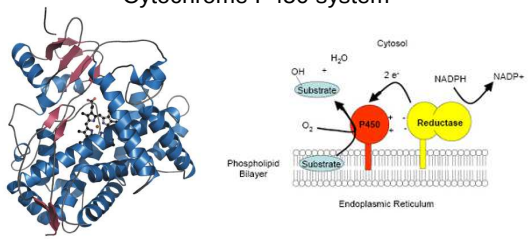
glutathione S-transferases
UDP-glucuronyltransferase
acetyltransferases

Purpose – inactivate, increase water solubility and excrete

Phase I & Phase II Reactions



Cytochrome P450 system



- Detoxify compounds by inserting one oxygen atom (monoxygenases)
- Reductase (FAD and FMN) + cytochrome P450 (1:20 ratio)
- General reaction (S = substrate):
- $NADPH + H^+ + O_2 + S\text{-}H \rightarrow NADP^+ + H_2O + S\text{-}OH$
- Example: Metabolism of ethanol by CYP2E1

Cytochrome P450 System

- Present in all cells except mature RBCs and skeletal muscle; high concentration in hepatocytes' microsomes
- Nomenclature derives from strong absorbance of reduced (carbon monoxide) haem protein with λ_{max} = 450 nm
- Over 100 genes encoding this family of proteins – *e.g.* CYP3A, CYP2C & CYP1A (4500 types in 2005)
- Genetic polymorphisms may exist in a given population, leading to different forms of a cytochrome P450 gene (good poor metabolisers)
- +participate in metabolism of hydrophobic endogenous compaunds: steroid hormones, cholesterol, fatty acids

Cytochrome P450 System

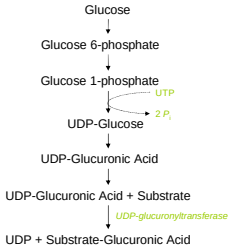
- The synthesis of the cytochromes P450 is inducible
- Induction occurs at either the transcriptional or post-translational level
- For example, polycyclic hydrocarbons bind to a cytosolic receptor called the aryl hydrocarbon receptor, which induces CYP1A1 and CYP1A2
- Drugs which are co-administered and metabolised by the same cytochrome P450 system can lead to altered metabolism of one or both of the drugs
  - Rifampicin is a CYP3A4 inducer. When co-administered with the oral contraceptive, it leads to increased metabolism of the latter drug, leading to decreased effectiveness
  - Ethanol induces CYP2E1, which can also metabolise acetaminophen to a toxic product which causes liver damage

Phase II Reactions

- Introduce a solubilising group to substrate
- This produces a more polar (water soluble) compound which can be excreted
- Examples:
  - Glucuronic acid (glucuronate)
  - Glutathione
  - Some amino acids (*e.g* Gly or Gln
- +methylation, acylation, sulfonylation, etc

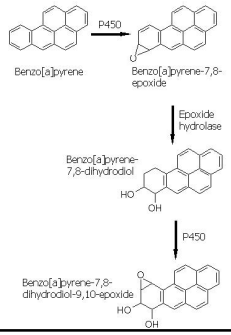
Glucuronic Acid

- Initially formed from glucose
- Conjugates with endogenous and exogenous compounds forming 'glucuronides'
- Reaction is catalysed by UDP-glucuronyltransferase (present in ER)
- Glucuronides are acidic and have a high solubility at physiological pH
- Involved in the metabolism of bilirubin

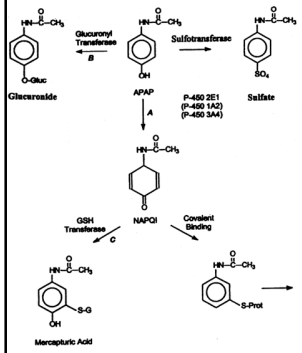


Metabolism of Benzo[a]pyrene

- Benzo[a]pyrene is a xenobiotic produced by burning coal, combustion of tobacco, barbequed food etc.
- It is a weak carcinogen
- Binds to aryl hydrocarbon receptor inducing cytochrome P450
- It is oxidised to a stronger carcinogen in mammals – benzo[a]pyrene-7,8-dihydrodiol-9,10-epoxide



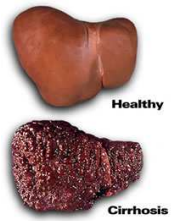
Metabolism of acetaminophen (Tylenol, Paracetamol)

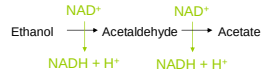


At normal doses, sulfate or a sugar is attached to OH and the drug is easily removed by the kidney.

At high doses, upper pathways cannot keep up and a liver P450 converts acetaminophen to a toxic metabolite which causes immediate liver damage.

Liver and acohol





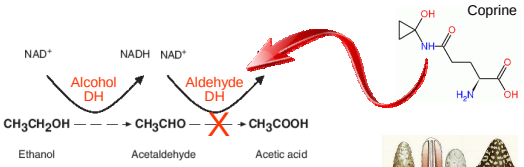
Two systems to metabolise ethanol:

Alcohol dehydrogenase (ADH) (i) and microsomal cytochrome P_{450} (ii)

In healthy person most of ethanol is metabolised by ADH with NADH production

Small proportion of ethanol is metabolised by the microsomal Cytochrome P_{450} system with oxygen consumption and ROS production.

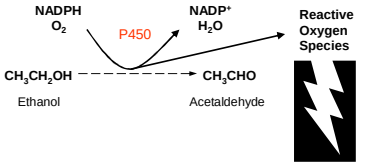
ADH route of metabolism of ethanol



Coprine

The poisonous effects of *Coprinus* mushrooms are caused by a molecule named coprine Coprine is harmless unless ingested within a few days of consuming alcohol. It covalently binds to aldehyde DH inhibiting that enzyme. It results in accumulation of acetaldehyde and symptoms similar to being "hung over".

P450 route of metabolism of ethanol



DNA, protein and membrane damage

Liver and acohol

Ethanol +NAD⁺ → Acetaldehyde + NADH + H⁺ (Alcohol DH reaction)

Pyruvate + NADH + H⁺ → Lactate +NAD⁺ (Lactate DH reaction)

Ethanol + Pyruvate → Acetaldehyde + Lactate Sum

Oxidation of alcohol produce NADH, that shifts equilibrium in Lactate DH reaction towards lactate formation. It inhibits gluconeogenesis since pyruvate level is depleted.

If food intake is restricted – low glucose in blood + gluconeogenesis is inhibited ⇒ no glucose for brain function.

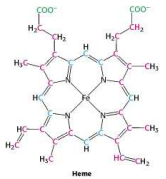
On the long run – high level of NADH inhibits oxidation of fatty acids ⇒ accumulation of fat and development of "fatty liver"

Summary

- The liver is the major site of detoxification in mammals
- Reactions are divided into two groups: Phase I and Phase II
- All reactions seek to increase the solubility (and hence excretion) of xenobiotics and endogenous compounds
- Some reactions of the cytochrome P450 system produce toxic metabolites, which additional pathways have evolved to deal with

Bilirubin production

Heme (porphyrin + Fe)



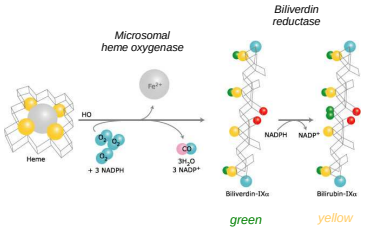
Protein	Function
Hemoglobin	Transport of oxygen in blood
Myoglobin	Storage of oxygen in muscle
Cytochrome *c*	Involvement in electron transport chain
Cytochrome P450	Hydroxylation of xenobiotics
Catalase	Degradation of hydrogen peroxide
Tryptophan pyrrolase	Oxidation of trypotophan

Coloured, fluorescent and redox-active

Erythrocyte life-time is 120 d – what is going on with haemoglobin later?

1–2 × 10^8 erythrocytes are destroyed per hour = ~ 6 g of hemoglobin per day

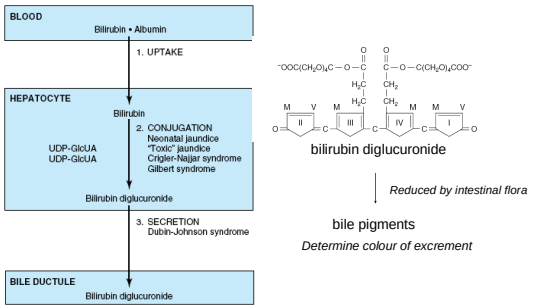
Heme metabolism



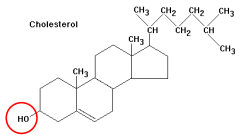
Bilirubin formed in peripheral tissues is transported by plasma albumin to the liver where:

1. uptake of bilirubin by liver parenchymal cells
2. conjugation of bilirubinwith glucuronate in the ER
3. secretion of conjugated bilirubin into the bile.

Heme metabolism



Cholesterol



Steroid which modulates the fluidity of cell membranes and precursor of progesteron, testosterone, estradiol and cortisol.

Animal products – eggs
Absorb about 50%
Excrete – 1 g/day (bile acids)

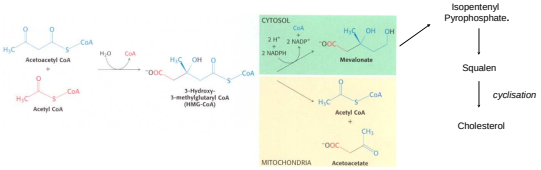
Assume 400 mg intake / day ⇒ 200 mg is absorbed
If 1000 mg is excreted ⇒ 800 mg from *de novo* synthesis

Lowering cholesterol in diet has very little effect on blood cholesterol !!!

Cholesterol Synthesis

- Occurs in cytosol
- Requires NADPH and ATP
- Highly regulated via HMG-CoA reductase
- 80 % in liver, ~10% intestine, ~5% skin

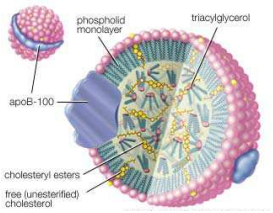
•Transcription
•Translation
•Degradation
•Phosphorylation)



Cholesterol transport

Highly hydrophobic – impossible to transport in form of aqueous solution

- Complexes of lipid and protein (mostly apoprotein)
- Central core of non-polar lipids (ChE & TG)
- Surface monolayer of polar lipids (mostly PL with some free Ch) interspersed with apoproteins
- Different combinations of lipid and protein gives rise to five main classes of lipoprotein
- Typically classified according to their hydrated density



Lipoprotein Classification I

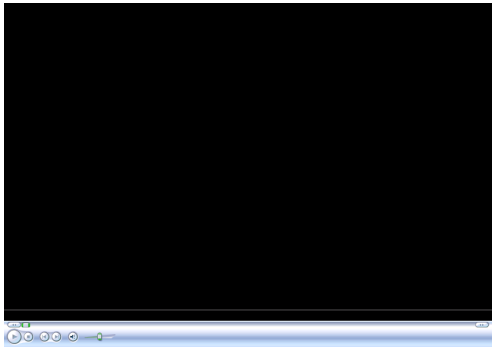
Hydrated Density

Lipoprotein	Abbrev.	Diameter (nm)	Density (kg/L)
Chylomicrons	CM	500	< 0.96
Very Low Density Lipoproteins	VLDL	43	0.96 – 1.006
Intermediate Density Lipoproteins	IDL	27	1.006 – 1.019
Low Density Lipoproteins	LDL	22	1.019 – 1.063
High Density Lipoproteins	HDL	8	1.063 – 1.210

Metabolism of Cholesterol

- Excess cholesterol is delivered to the liver *via* reverse cholesterol transport - multi-step process resulting in the net movement of cholesterol from peripheral tissues back to the liver via the plasma compartment
- This is converted to cholic acid or chendeoxycholic acid (bile acids) which are released into the ileum
- The bile acids are converted to deoxycholic acid and lithocholic acid, respectively, by bacterial hydrolases
- When they return to the liver (*via*. the enterohepatic circulation) they are conjugated
  - Deoxycholic acid + Glycine → Glycholic acid } Gallbladder
  - Deoxycholic acid + Taurine → Taurocholic acid
  - Lithocholic acid + SO_4^{2-} → Lithocholic acid-sulphate ester → Excreted

Atherosclerosis



Summary

- Lipids are combined with apoproteins for transport around the body
- Dietary lipids first move though the exogenous pathway to the liver
- Lipids are exported from the liver *via*. the endogenous pathway
- Reverse cholesterol transport returns excess cholesterol to the liver
- Atherosclerosis is a low-level inflammatory condition characterised by cholesterol-enriched macrophages in the arterial intima