The Liver
General Metabolism

Dr Alexander Galkin
Level 2 Mammalian Biochemistry

Contact Details

Email: a.galkin@qub.ac.uk

Office: MBC Room 01.442

Tel: (028) 90972166

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 hepatocytes
3. Be able to describe the liver's role in glucose homeostasis and direct and reverse reactions

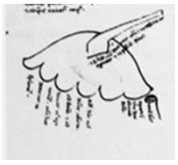
History

Aristotle, 350 B.C.E

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

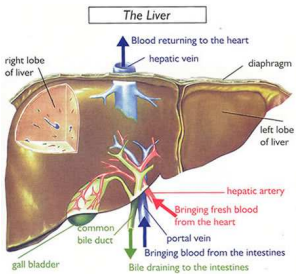
Galen, 200 A.D.

"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."



The Liver

- Largest internal organ of the human body with highest temperature
- Segmented structure comprising four main cell types
  - Hepatocytes (parenchyal 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
- 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
- Transmination 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}

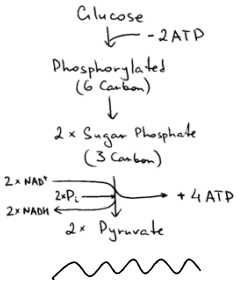
Coagulation Factors
- Synthesis of fibrinogen, prothrombin and Factor VII

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

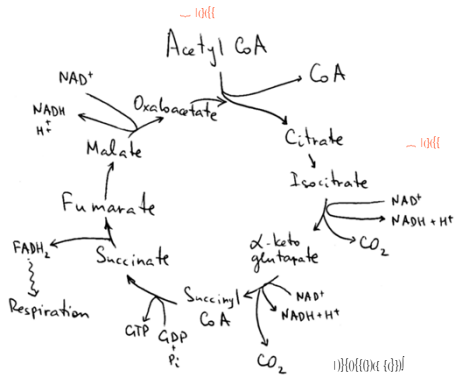
Metall ions storage
- Hepatocytes capture iron (apoferritin) and store it as ferritin
- Copper

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

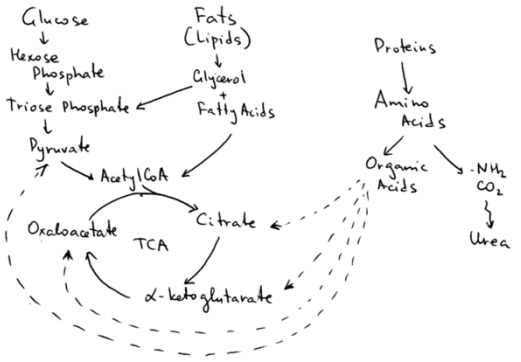
Carbohydrate Metabolism



Krebs cycle (TCA cycle)

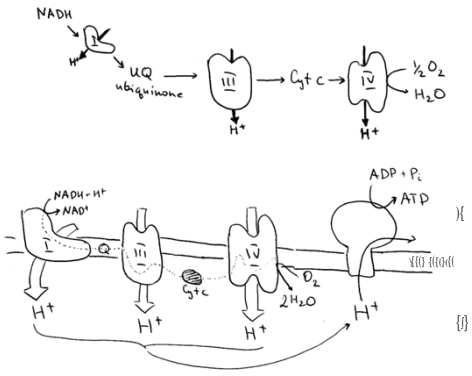


Metabolic network

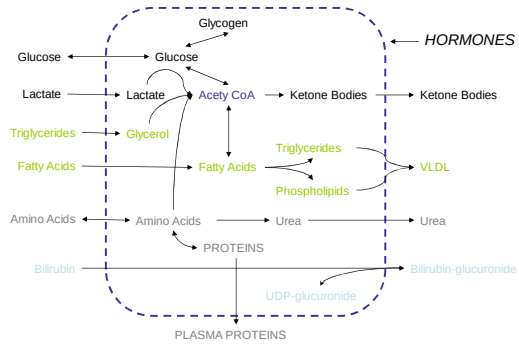


Unification of substrates

Respiration and ATP synthesis



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

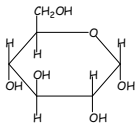
Lipogenesis, the production of triglycerides (fats)

Cholesterol synthesis

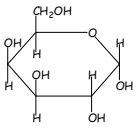
Haemoglobin breakdown → bile production

Detoxification of xenobiotics

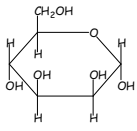
Common hexoses



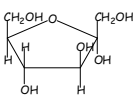
a-D-Glucose



a-D-Galactose



a-D-Mannose

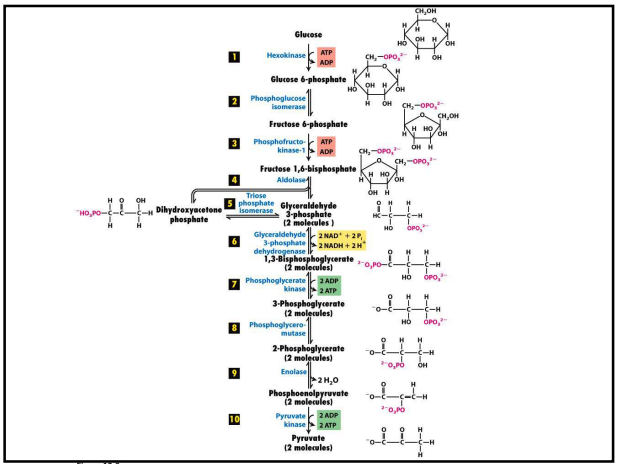


a-D-Fructose

+di and oligosacchrides

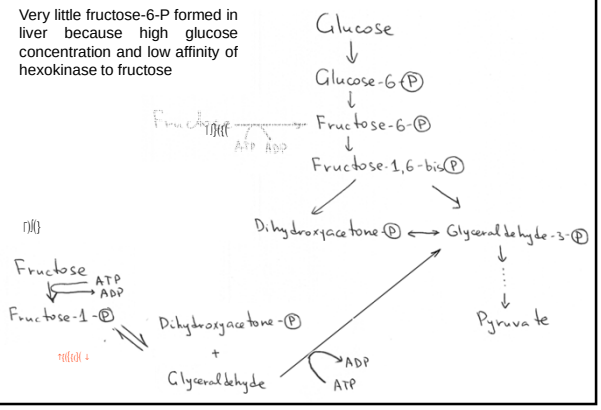
Common hexoses

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 $\rightarrow$ Fructose-1-P + ADP
ADP + P_i $\rightarrow$ ATP *(in oxidative phosphorylation)*

Fructose + P_i $\rightarrow$ Fructose-1-P

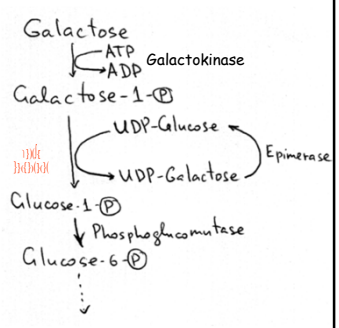
P_i is tied up to fructose $\Rightarrow$ Depletion of P_i $\Rightarrow$ impossible to make ATP from ADP

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

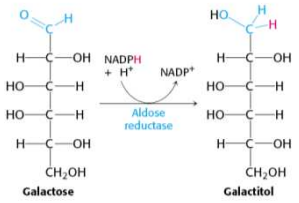
Galactosemia

- 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
- Un-metabolised galactose is reduced to galactitol (cataract formation & CNS damage)
- Accumulation of galactose 1-P leads to liver damage



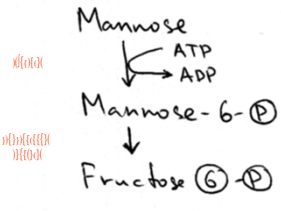
Galactosemia

Cataract formation



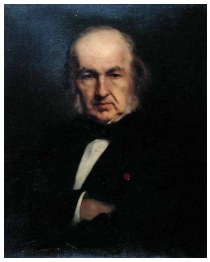
Treatable by diet, however, in the most galactosemic patients (especially if transferase is affected) this treatment does not prevent development of late-onset complications: mental retardation, ovarian failure and neurologic disturbances (nerve tissue glycolipids)

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 - that 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!

~~One organ-one function~~

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 160 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 gycerol

Glycerol $\xrightarrow{ATP\ ADP}$ Glycerol-P $\xrightarrow{NAD^+\ NADH}$ Dihydroxyacetone-P

Lactate $\xrightarrow{NAD^+\ NADH}$ Pyruvate

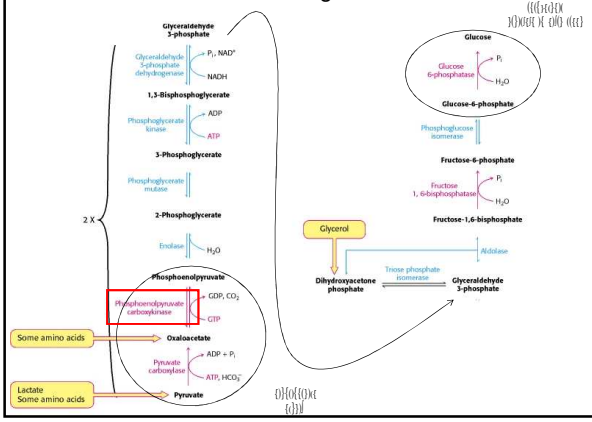
Amino Acids $\xrightarrow{transamination}$ Oxaloacetate / Pyruvate

Gluconeogenesis. Precursors.

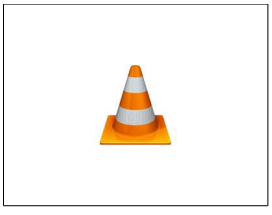
Lactate, Amino Acids and Glycerol

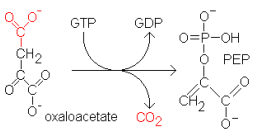
- Lactate returns to the liver, is re-oxidised to pyruvate and fed into gluconeogenesis. The combination of glycolysis in peripheral tissues with hepatic gluconeogenesis is referred to as the Cori cycle
- Some amino acids are directly converted to glucose (glucogenic amino acids); others are first converted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

Gluconeogenesis



Super mouse

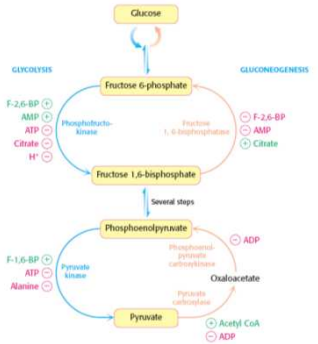




Phosphoenolpyruvate carboxykinase

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 agressive

Glycolysis and gluconeogenesis regulation



Direct and reverse reaction – futile cycle - flux control

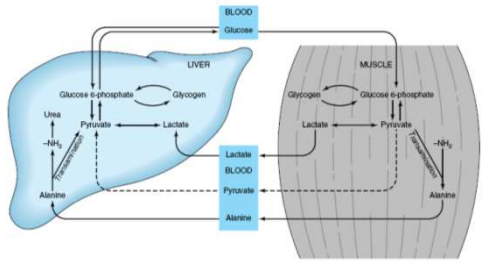
Cori and alanine cycle

Cori cycle = glucose-lactate cycle

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

Lactate – Muscle and red blood cells

Alanine - muscle in starvation



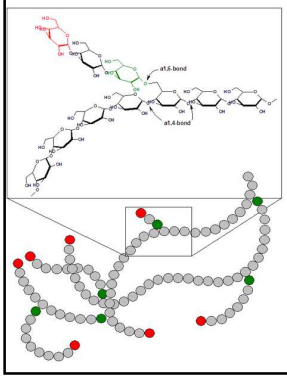
Different isoforms of enzymes catalyse forward and reverse reactions in different tissues

Who are these people?!?!

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

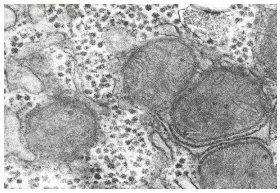


Glycogen - branched polymer of glucose, readily mobilized storage of glucose

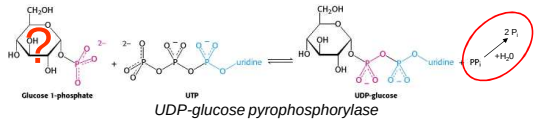
α-1,4-glycosidic and α-1,6-glycosidic linkage

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

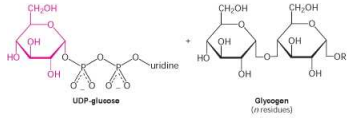
Molecules up to ~ 2×10^7 Da in glycogen granules in liver ~200-400Å



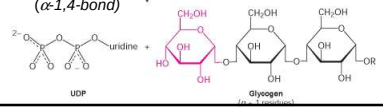
Glycogenesis



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 accessability (synthesis/degradation rate). Special, very specific branching enzyme α-1,4-glucan-6-glycosyltransferase catalyses that reaction.

Glucose 6-phosphate ⟶ glucose 1-phosphate (1)

Glucose 1-phosphate + UTP ⟶ UDP-glucose + PP_i (2)

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

UDP-glucose + $glycogen_n$ ⟶ $glycogen_{n+1}$ + UDP (4)

UDP + ATP ⟶ UTP + ADP (5)

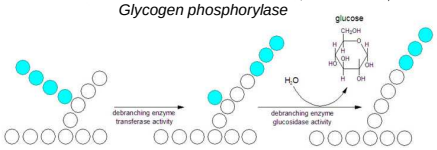
Sum: Glucose 6-phosphate + ATP + $glycogen_n$ + H_2O ⟶ $glycogen_{n+1}$ + ADP + $2\,P_i$

Glycogen degradation

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

Glycogen phosphorylase

Ia



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

II glucose 1-phosphate ⟶ Glucose 6-phosphate

Phosphoglucomutase

III Glucose 6-phosphate + H_2O ⟶ glucose + P_i *liver specific enzyme located in ER*

Glucose 6-phosphatase

Carbohydrates entry to glycolysis

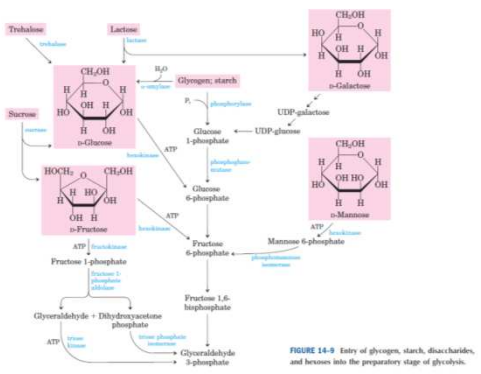


FIGURE 14-9 Entry of glycogen, starch, disaccharides, and hexoses into the preparatory stage of glycolysis.

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

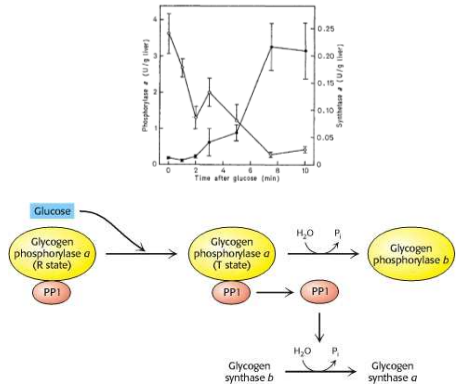
– Allosteric – Phosphorylase inhibitor - ATP, G6P and glucose

Glycogen synthase

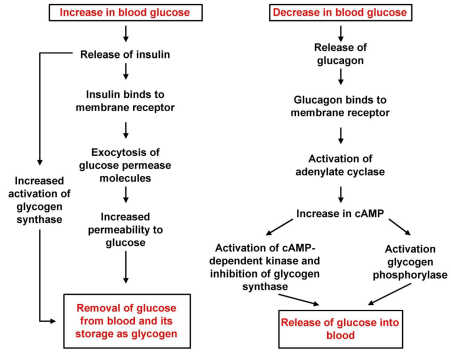
– Covalent - phosphorylated by kinase at C and N terminals increases net charge from -13 to -31
- active (a) form is dephosphorylated
- inactive (b) form is phosphorylated

– Allosteric – Synthase activator – Glucose

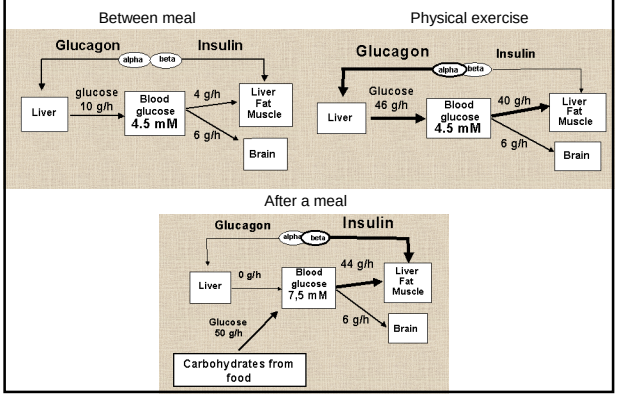
Glycogen phosphorylase *vs.* synthase



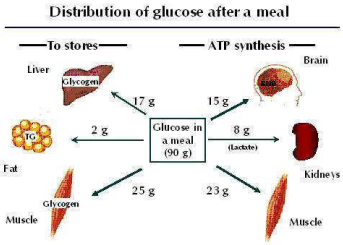
Blood glucose



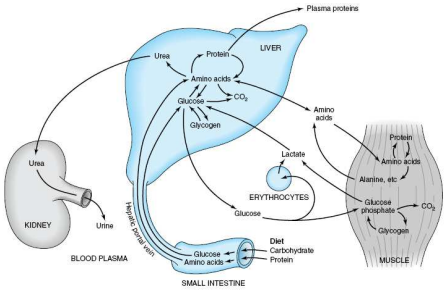
Blood glucose



Blood glucose



Liver's Role in Metabolism



Summary

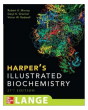
- The liver plays a key role in mammalian metabolism – the laboratory of the human body
- The liver has an especially important role in glucose homeostasis = glucose synthesis and glycogen synthesis/degradation/storage
- Direct and reverse reactions are directed via different pathways
- Disruption of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