Topic A: Regulation of metabolism

Objective	Related information
Lecture 1: Metabolic pathways in the liver and fuel distribution to tissues	

Central Role of the Liver
 	
NOTE:
CAC = citric acid cycle = TCA = tricarboxylic acid cycle = Krebs cycle
	• The liver adapts to changing metabolic conditions
	  ○ Portal vein carries nutrients to the liver
	  ○ Hepatocytes turn nutrients into fuel
	  ○ Hepatocyte enzymes turn over quickly
	  ○ Enzymes increase or decrease with changes in diet and needs of other tissues
	• Liver functions
	  ○ Provide glucose and ketones for other organs
	  ○ Process amino acids into urea
	  ○ Store nutrients
	  ▪ Iron
	  ▪ Fat soluble vitamins (e.g. vitamin A)
	  ○ Detoxify and solubilise organic compounds via cytochrome P450 system
	  ▪ Drugs
	  ▪ Food additives
	  ▪ Preservatives
	  ○ Serves as a distribution centre
	  ▪ Exports nutrients in the correct proportions to other organs
	  ▪ Smooths fluctuations in metabolism caused by intermittent food intake
	  ▪ Processes excess amino acids → urea
	  ▪ Sends other wastes to the kidneys
	The liver
	• Processor and distributer of nutrients to other tissues
	• After a meal
	  ○ Liver is bathed in blood full of nutrients, glucose and elevated insulin levels
	  ○ Liver takes up carbohydrates, lipids and amino acids
	  ▪ Metabolised these then stores or sends them on
	• Smooths out potentially broad fluctuations in nutrient availability to peripheral tissues
	• Central role in nutrient distribution
	• Metabolic flexibility
	  ○ Example
	  ▪ Diet rich in proteins
	  ▪ Influx of amino acids will be used for plasma and tissue proteins
	  ▪ OR, catabolised to synthesise intermediates → citric acid cycle
	  ▪ After this meal, liver enzymes start to synthesise enzymes relevant to CHO metabolism and fat synthesis
	  ▪ Extra-hepatic tissues adjust metabolism to these conditions
	• Other sugars processed by the liver
	  ○ Fructose, galactose, mannose → G-6-P
	  ○ G-6-P is the transfer station in the liver
	  ▪ Multiple fates
	  ▪ Fates depends on the needs of the tissues
	Hepatocytes
	• GLUT2 transporters
	  ○ Allows rapid passive diffusion of glucose in and out
	  ○ Thus the concentration of glucose in the hepatocyte is the same as in the blood
	• Have glucokinases (= hexokinase IV)
	  ○ Higher K than other hexokinases
	  ▪ 10mM vs 4mM
	  ▪ So glucose-6-phosphate (G-6-P) isn't made when glucose is low → when other tissues need it
	  ○ Not inhibited by G-6-P
	  ▪ Thus G-6-P can be continuously made
	  ▪ Also continues to phosphorylate at concentrations that would overwhelm other hexokinases
	• Glucose entering the hepatocyte is phosphorylated by hexokinase IV (= glucokinase) to yield glucose-6-phosphate
	  ○ Fructose, galatose and mannose are also converted to glucose-6-phosphate
	• Depending on the metabolic needs of the body G-6-P will take varying pathways
	  ○ Occurs by the action of several allosterically regulated enzymes and hormones directing the glow of glucose
	Fates of G-6-P in the liver
	• Options
	  ○ Dephosphorylated → free glucose to send to other tissues
	  ○ Made into liver glycogen
	  ○ Enter glycolysis → pyruvate → Acetyl CoA → CAC → ATP
	  ○ Enter glycolysis → pyruvate → Acetyl CoA → fatty acids → TAGs
	  ○ Enter pentose phosphate pathway → NADPH and ribose-5-phosphate
	  ▪ Can make nucleotides from ribose-5-phosphate
	• The pathways chosen will depend on the metabolic needs of the body, regulated by allosterically regulated enzymes and hormone

Metabolism of Amino Acids in the Liver

- Made into proteins for the liver and other tissues
- Made into hormones or nucleotides
- Make into CAC intermediates or pyruvate
  - For gluconeogenesis
  - Convert pyruvate → Acetyl CoA
    - Liver cell energy
    - Conversion to lipids
- Amino acids in the liver follow several metabolic routes
  - Precursors for protein synthesis
    - Liver constantly renews its proteins → high turnover
  - To synthesise plasma proteins
- Exported to other tissues for synthesising proteins
- Forms nucleotides, hormones, nitrogenous compounds
- Amino acids not needed for biosynthetic reactions are deaminated, degraded to pyruvate and CAC intermediates → various fates
  - Ammonia → urea
  - Pyruvate → glucose and glycogen via GNG
  - Oxidised → Acetyl CoA → oxidised in the CAC, oxidative phosphorylation to ATP or converted to fatty acids and TG for storage
  - CAC intermediates → glucose via GNG
- Increased amino acid degradation
  - In the absorptive state
    - More amino acids present in the liver than can be used for protein synthesis or nitrogen products
  - Excess amino acids cannot be stored
    - Released into the blood for other tissues
    - Used by tissues for protein synthesis or deamination
      - After deamination, C-skeleton is degraded by the liver → pyruvate → Acetyl CoA → CAC intermediates
    - Metabolites are oxidised for energy or fatty acid synthesis
- Increased protein synthesis
  - Body cannot store proteins like glycogen or fats
  - There will be replacement of proteins previously degraded
    - However no net increase in stores

Metabolism of Fatty Acids in the Liver

- Acetyl CoA and NADH
  - → CAC and oxidative phosphorylation → ATP
    - Fatty acids are the primary fuel for the liver
  - Excess acetyl CoA
    - → Ketone bodies for the brain, heart, etc. in carbohydrate restriction and fasting
  - Some acetyl CoA → cholesterol
- Make phospholipids → bilayer
- TAGs for storage
- Transported to other tissues for oxidation
- Fate of fat entering the liver
  - Conversion to liver lipids
  - Fatty acids → primary oxidative fuel for the liver
    - Under most conditions
    - Free fatty acids may be oxidised by beta-oxidation to yield Acetyl CoA and NADH
  - → Acetyl CoA → Oxidised via CAC and oxidative phosphorylation → ATP
    - Excess acetyl CoA → acetoacetate and hydroxybutyrate (ketones)
      - Ketone bodies can penetrate the blood-brain barrier
      - Provide the brain with acetyl CoA for oxidative reactions
      - Can supply a third of energy required by the heart
      - Provides 60 – 705 of energy required by the brain during fasting
    - Some Acetyl CoA
      - → Precursors of cholesterol, steroid hormones and bile salts
      - Cholesterol is important for membranes and bile salts, essential for digestion and absorption of fats
  - Fatty acids → plasma lipoproteins
    - Carry lipids to other tissues (e.g. adipocytes for storage)
    - Some Fas are bound to albumin and transported to the heart and skeletal muscle → oxidised → fuel
- Increased fatty acid synthesis
  - Liver is the primary tissue for de novo synthesis of fatty acids
  - Synthesis is favoured by
    - Availability of substrates (e.g. acetyl CoA)
    - Activation of acetyl CoA carboxylase
- Increased triacylglycerol synthesis
  - TG synthesis favours given fatty acyl CoA is available from synthesis of acetyl CoA
  - Glycerol-3-phosphate is available in abundance → glycolysis is increased
    - This is the backbone for the formation of TG
  - Liver packages TG → VLDL → blood → extra-hepatic tissues
    - E.g. to adipocytes and muscle