Lecture 9 – Metabolism of Obesity + Type II Diabetes

Cholesterol + Triglycerides

- "Good" vs "bad" cholesterol
    - Not the cholesterol itself – it's what **lipoprotein particles** they're packaged in
        - **LDL** and **VLDL** – distributors of fatty acids/cholesterol **around the body**
        - **HDL** – delivers cholesterol **back to the liver**

Cholesterol

- Important in our **membranes** (lipid raft formation etc – thicker region where we find receptor/signalling molecules) – fundamental to function
- Synthesis of **steroid** hormones
- Important for formation of **bile**
- **Cholesterol esters** – modified version of cholesterol that changes its solubility

Triglycerides
aka triacylglycerol, TAG

- Glycerol backbone + 3 fatty acids
  Many types of TAGs depending on what fatty acids are attached
- Lipids are transported in **lipoprotein particles**
    - **Apolipoproteins** are the protein components – **structural scaffold**
        - Size/shape of particle depend on what apo-lipoproteins are involved
    - **Phospholipid monolayer** surrounding triglycerols, cholesterol esters

4 different types of lipoprotein packages

- Chylomicrons
- VLDL
- LDL
- HDL

Differ by their density + composition + sizes

Dietary Fats

Gall bladder produces bile – emulsifies fats

Free fatty acids + TAGs ingested
Lipases turn TAGs into free fatty acids

Cells on **intestinal surface** package them to make **chylomicrons**
Chylomicrons take the dietary fats from the **gut** to the **liver**

Tissue specialization

Muscle:

- Fuel sources: glucose, fatty acids, ketone bodies
- Fuel stores: muscle stores **75%** of total body glycogen (>5MJ) + can represent 1% of muscle weight after a meal
  Remaining **25%** glycogen stored in the **liver**
- **Resting** conditions = use **fatty acids** as major fuel source (**85% energy**)
  (Don't want to use up glycogen at rest)
    - Fatty acids undergo **β-oxidation** instead of glycolysis

    - Chop off **pairs** of carbons (pairs of CH2 or CH3) on the fatty acid chain to be metabolised as **acetyl-coA** in the citric acid cycle
    - This also generates **NADH**, **FADH2** – go to oxidative phosphorylation in the mitochondria
- Heart muscle prefers to use **acetoacetate** more than glucose (**ketone** bodies)

4 fat pathways

1. **Enterohepatic pathway**

- **Cholesterol** is precursor for **bile** salts
- Secreted from the liver in bile salts used to emulsify fats
- Bile can be reabsorbed and returned to gall bladder

2. **Exogenous pathway**

- For dietary fats + delivering free fatty acids to tissues that need high energy/fats
- After emulsification + breakdown, free fatty acids absorbed by enterocytes
- Packaged into triacylglycerol → **chylomicrons**
- Chylomicrons move through circulation to the liver
- Free fatty acids **dropped off** along the way – to **myocytes**, **adipose**, **mammary gland**
    - Need high energy + fats
- The depleted chylomicrons end up at liver + drop off the remnants of the triacylglycerol (**degraded in lysosomes**)

3. **Endogenous pathway** ("bad" pathway – **delivering** free fatty acids + cholesterol TO tissues)

- When diet has **excessive** fatty acids + cholesterol (+ carbohydrates that get turned into TAG) (Carbs, amino acids and fat can interconvert in the body)
- Free fatty acids → TAGs and cholesterol → cholesterol esters
- Cholesterol + free fatty acids in liver packaged into **VLDL** for delivery up to tissue again for **storage**
    - To adrenal gland, gonads, muscle, adipose
- After the free fatty acids are dropped off, the VLDL → **LDL**
    - LDL = **rich in cholesterol**/cholesterol esters
- LDL carries cholesterol to **tissues** (muscle, adrenal gland, adipose) and **macrophages** (become foam cells)
- They circulate back to the **liver**, received by **LDL receptors** to recycle contents
    - Cholesterol goes into membranes
    - Bile acids are stored as **cholesterol esters** in liquid droplets

Insulin affects the flux of the system:

- Insulin high (fed state) = VLDL moves dietary lipids **to adipose** for **storage**
- Insulin low = VLDL moves lipids **from adipose** to **muscle** for oxidation to make energy (via circulation)

4. **Reverse cholesterol pathway** ("good" pathway)

- HDL particles (originate from the liver/small intestine) pick up cholesterol from the periphery and bring them back to the **liver**
    - **Extra-hepatic** tissues - important ones are **macrophages** + **foam cells** (macrophages that picked up a lot of lipids)
- Received by **HDL receptors**
- Cholesterol dropped off and packaged into **VLDL** to be sent out again

Formation of atherosclerotic plaques

Lots of **extra lipids** in blood → atherosclerotic plaques

1. Arterial wall gets damaged by **oxidised lipoproteins**
   They **aggregate** + **stick** to extracellular matrix
2. Attract/activate monocytes → **macrophages**
3. Macrophages ingest lipoproteins to become **foam cells**
4. Foam cell accumulates **cholesteryl ester droplets**
5. Tissue damage, necrosis, apoptosis
6. Formation of plaque
   At low levels, won't notice but at some point will occlude the lumen of the blood vessel and stop blood flow

Can be **reversed by HDL** – can **pick up** cholesterol from plaque and bring it back to liver
Is why HDL is "good"

i.e. it's not the cholesterol itself that's good or bad, it's what it's **packaged** in

Carbohydrates + Fats

Quick overview of breakdown:

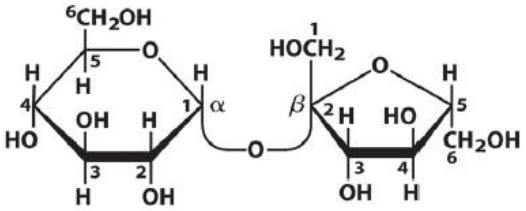
- Glycolysis: phosphorylated, converted to fructose, phosphorylated, split into 3 carbon sugars (trioses)
- Citric acid cycle: Amino acids, fatty acids, pyruvate, can all enter this process – reduce to NADH, FADH2
- Oxidative phosphorylation

Sucrose vs Fructose

Sucrose is **similar in composition** to HCFS55
– even though we don't use HFCS55 in our foods, the sucrose in cane sugar can also cause similar problems

Sucrose = glucose + fructose

Glucose and fructose are structural isomers



Fructose = many varieties of HFCS
Names depend on how much fructose they contain

- HFCS55 = 55% fructose (once water is extracted) – mostly in soft drinks (most commonly used)
  - **Same amount** as sucrose – 50% glucose, **50% fructose**
- HFCS42 = 42% fructose – beverages, processed foods, cereals, baked goods
- HFCS65 = 65% fructose – some soft drinks
- HFCS90 = 90% fructose – mixed with HFCS42 to make HFCS55

Sweetness of fructose = **1.7x sweeter** than sucrose

Glucose + fructose metabolism are **interconnected**, **overlapping + different**

For fructose, can either

- Phosphorylate (with **hexokinase**) to make **fructose-6-phosphate**
  - Goes down the same **glycolysis** pathway as glucose
  - Becomes fructose-1,6-bisphosphate
  - Then cleaved to become **triose sugars**
  - The triose sugars can **interconvert**
- Phosphorylate (with **fructokinase**) to make **fructose-1-phosphate**
  - Split by **aldolase** to get **glyceraldehyde + dihydroxyacetone**

        - Glyceraldehyde can be made into **glycerol**
            - i.e. we make the **backbone for fat** out of **fructose**
        - Glycerol can be phosphorylated to be part of TAGs
        - Can get glyceraldehyde with glucose too, but in the **liver (hepatocytes)** is where you have enzymes for **fructose**
    - Become **glyceraldehyde 3-phosphate**
        - Continues into glycolysis
        - Can become **fatty acids**