Digestion and transport of TAG by plasma lipoproteins

Lipoproteins are multimolecular complexes of lipids and proteins, they are not macromolecules.

They transport lipids in the plasma because lipids are insoluble in water and plasma is mainly formed of water, these lipids include:

1- TAG+cholesteryl esters (CE):
neutral lipids, nonpolar, hydrophobic (in the core of the lipoprotein)

2- Cholesterol+phospholipids: amphipathic molecules (hydrophilic+hydrophobic).

The prefix apo-means the protein part that is bound to something else ex (apoenzyme is the protein part of the enzyme).

Apolipoprotein (or apoprotein) is the protein part of lipoproteins.

They are amphipatic molecules having both hydrophobic region (to interact with lipids) and hydrophilic region (on the surface).

Note: The doctor said that they are considered surface components if the lipoprotein.

They include several classes (apolipoprotein A, B, C, E, ...)

Functions of all lipoproteins are not known yet, but some have a: 1- structural role: maintenance of the structure of lipoprotein particles.
2- regulatory role: regulation of enzymes’ activity in the metabolism of lipoproteins.

And some of them are required for binding to surface receptors.

The chemical representation of lipoprotein particle (2 regions)

. Surface (amphipathic): free cholesterol (unesterefied cholesterol), [because of OH group on cholesterol it’s on the surface], phospholipids [amphipathic, hydrophilic region on surface], apolipoprotein.

. Core region (hydrophobic): cholesteryl esters + TAG

We are not supposed to memorize the numbers so I didn’t mention them

Plasma lipoproteins are classified into 5 major classes based on their density:

. Chylomicrons lowest density, less than water.

. Very-low density lipoproteins (VLDL).

. Intermediate-density lipoproteins (IDL): are intermediate between VLDL and LDL.

. Low-density lipoproteins (LDL)

. High-density lipoproteins (HDL)

What determines the density is the ratio of protein to lipid; lipoproteins are denser and smaller as the protein to lipid ratio increases.

(Proteins ‘density is higher than the density of water while lipids ‘density is lower)
so chylomycrons has lowest percentage of protein

HDL has highest percentage of protein.

Particles within each class differ lightly in their densities due to differences in their composition, that's why each class has range of densities.

The major lipid indicates the function of each class; chylomicrons' function is the transport of TAG, LDL particles transport cholesterol

VLD : TAG is the major component

HDL function is transport of cholesterol [according to the dr].

Lipoproteins contain apolipoproteins.

All classes except HDL have apolipoprotein B.

The apolipoproteins A is found only in HDL.

Function of transport:

1- chylomicron transport dietary lipids

2- VLDL transport endogenous TAG (synthesized in the liver from excess carbohydrates or excess proteins)

3- LDL and HDL transport cholesterol.

Note: the percentages in the slides are not exact because they are continuously changing due to continuous metabolism.

**The surface area to volume ratio restricts the size:**

Large particles: Low surface area to volume ratio.

Small particles: high surface area to volume ratio.
(i.e: the higher the surface area the lower the volume)

Chylomicrons are the largest in size and HDL are the smallest. Diameter varies from 100 Ang=10 nm to 1 micrometer.

In chylomicrons the surface components’ (proteins, phospholipids) percentage is small, while TAG’s (core component) percentage is big.

Lipoproteins can be separated based on their density by centrifugation (expensive). But electrophoresis is easier. Lipoproteins are also plasma proteins. The plasma sample we use contains plasma proteins as well so we use a special stain that reacts only with lipids so that we see only the separated lipoproteins.

Electrophoresis does not depend on the density it depends on the ratio of the charge to the mass.

Observations after separation by electrophoresis:

. Chylomicrons remain at the origin, they don’t move because the protein percentage is very small 1% [thus, the charge is small] and their size is very large so their mobility is almost zero.

. HDL are the fastest because they have a high proteins percentage and a small size.

Based on the migration (electrophoresis mobility) HDL are called alpha lipoproteins [because it migrates with alpha albumins], LDL beta and VLDL pre beta.

(Electrophoresis is useful for everyday use in hospitals, labs)
Digestion of dietary lipids is the hydrolysis of one or more fatty acids from the lipid particles (ester bond).

The TAG molecule is too large to enter the Entercocytes (intestinal absorptive cells).

So the hydrolysis of at least two fatty acids occurs before they can be absorbed from the small intestine.

Cholesteryl ester which is cholesterol esterified to fatty acid, is hydrolyzed with water to free cholesterol and fatty acid.[in small intestines].

This type of reaction requires water to be able to attack ester bonds. So TAG (Which is insoluble in water) should be found in a soluble form to be able to interact with water.

This solubility problem is solved by using an emulsifier (a Solubilizing agent) bile acid (e.g: cholic acid) modified from cholesterol, oxidation of c#24 to carboxyl group & presence of additional –OH groups, so it has hydrophilic and hydrophobic regions. So these molecules can participate in formation of micelles.

Two emulsifiers that are usually used: Cholic acid and Chenodeoxycholic acid they are bile acids, carboxylic acids derived from cholesterol.

When linked to amino acids like glycine and taurine(sulfer containing), they become stronger acids(e.g. Glycocholic acid). They mainly exist in the salt (ionized form) form and are called bile salts. [differentiate between these and bile acids; which are unconjugated].
Bile salts have along hydrophobic region (steroid nucleus) and a terminal hydrophilic acid.

Because they are amphipathic molecules bile salts are able to make micelles, these micelles can accommodate TAG.

A micelle is a large number of amphiphatic molecules (bile salts phospholipids) and in the interior there is TAG.

Due to Peristalsis, pressure and movement in the small intestine (duodenum and jejunum) bile salts that are secreted from the bile and TAG are mixed together forming these mixed micelles (after fatty meal).

Lipase, an enzyme secreted by the pancreas, is attached to these micelles by the help of a protein called colipase (from pancreas).

TAG is now surrounded by amphipathic molecules and attached to lipase and co lipase, the surface area has increased to a large extent and interaction with water becomes possible ... so TAG can be hydrolyzed.

Cholesteryl ester hydrolyzed by an enzyme called cholesteryl esterase which removes the fatty acid on the carbon 3 to give free cholesterol + fatty acid.

Phospholipids hydrolyzed by phospholipases by the removal of:

One fatty acid from carbon 2 to give Lysophosphatidylcholine
Two fatty acids to give glycerylphosphorycholine. [this also occurs in the small intestine].
TAG is hydrolyzed by the removal of two fatty acids from carbon 1 and carbon 3 to give monoacylglycerol in which glycerol is esterfied to fatty acid at carbon 2. So it is named: “2-monoacylglycerol”.

If we inhibit these lipases digestion of fat will be incomplete or insufficient and as a result the absorption will be insufficient so they will be secreted in feces.

One of the anti obesity drugs (Orlistat), acts as an inhibitor for lipoprotein lipase.

When a person using this drug eats fat, fat will be secreted in the feces because TAG digestion will be impaired so it can’t be absorbed.

The digestion of TAG actually starts in the mouth and stomach where there are other lipases that are specific for short and medium chain fatty acids which are found in dairy products (Fatty acids, monoacylglycerol and cholesterol) together they form mixed micelles; these micelles are soluble in the aqueous environment of the small intestine.

When they come in contact with the intestinal mucosa cells (fatty acids, free cholesterol and phosphorylcoline) are transferred (diffused) into these cells. If there is a defect in pancreas, on digestion, also if bile isn’t secreted or isn’t able to reach the intestine, lipids will be secreted in feces.

Fat soluble vitamins are found in the core of mixed micelles so they are absorbed with fat during normal digestion of fat. If there is any defect in the digestion or absorption of fat, the absorption of fat soluble vitamins will be affected as well.
Lingual lipase is secreted from glands in the tongue.

Gastric lipase is secreted in the stomach.

These enzymes act on medium and short chain fatty acids. They are acid stable; they are denatured by the low pH in the stomach.

It is significant in neonates for the digestion of lipids in the milk which are their major source of energy (more than carbohydrates).

In pancreatic insufficiency if there is a disease in the pancreas one of the solutions is to increase dietary lipids that are found in dairy products.

**What happens to (monoacylglycerol, fatty acids, cholesterol) after being absorbed into the enterocyte?**

Monoacylglycerol accepts two fatty acids to be converted back to triacylglycerol.

Fatty acids to be used for the synthesis of TAG have to be converted to fatty acyl-CoA.

After digestion in the lumen of the intestine absorption takes place and TAG is produced again.

Cholesterol is esterified by fatty acid to make cholesteryl ester.

These hydrophobic non polar molecules aggregate together and become surrounded by apolipoprotein B-48 and phospholipids to form chylomicron particles.

Chylomicrons are very large (1200 nm in diameter) so if they were transferred to the blood capillaries immediately they will
block them, instead they are transferred by exocytosis to the lymphatic vessels through which they move to the thoracic duct and then to the subclavian vein.

Chylomicrons are synthesized in the small intestine then they are released to the blood (called nascent chylomicrons).

In the blood apolipoprotein CII and apolipoprotein E are transferred from HDL to chylomicrons.

Now chylomircs containing (apo B-48, apo C2, apo E) enter the capillaries of various tissues (adipose tissue, cardiac muscle, muscle, kidney, liver,…)

In the wall of the capillary there is an extra cellular enzyme called lipoprotein lipase it is firmly attached to the lumen of the capillary. It hydrolyses TAG into fatty acids and glycerol (apo C2 is the activator of this lipase).

Fatty acids are absorbed into the cell.

As TAG is being hydrolyzed chylomicron is shrinking in size and the protein percentage is getting bigger.

The apo C2 is returned back to HDL.

What remains is called chylomicron remnant which is smaller in size and higher density and contains: cholesteryl esters and other lipids, apo B48, apo E which is important for the uptake of these remnants by the liver through endocytosis (most important one is apo E).

Insulin help the synthesis of lipoprotein lipase.

Lipoprotein lipase are several isoenzyme at least 2 types: one formed in adipose tissue other formed in skeletal muscle and
they differ in $K_m$, muscle enzyme have lower $K_m$ so it has more priority.

'
they love me they make me stronger 
,they hate me they make me unstoppable '  
Cristiano Ronaldo

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