All fractions of lipoproteins transport cholesterol in blood because cholesterol is insoluble

Classes of lipoproteins:

|  |  |  |
| --- | --- | --- |
| **HDL** | **VLDL** | **Chylomicrons** |
| it's synthesized in Liver ,intestine as nascent discoid shape this shape is acquired because it's produced mainly from surface components (phospholipids ,Apo A1) or sometimes it's synthesized from plasma because free apoA1 is found and phospholipids so it'll be produced (thus the exact origin of HDL is not clear) | Liver | Small intestine |
| Cholesterol | 1-Mainly :TAG that is synthesized in liver is originally from excess carbohydrates (endogenous fat) 2-along with cholesterol | 1-TAG :dietary fat (exogenous fat) 2-Cholesterol  |
| Mainly apolipoprotein A1Note :it's required for the esterification2-Apo C & Apo E (given to other types such as:VLDL) | Apo lipoprotein C2 and ApoE(from HDL) | Apolipoprotein B48 |
| 1-They are very small particles, surface area is really small ,because of the high percentage of surface components of apolipoproteins and phospholipid thus increasing the ability to bind cholesterol2- maturation of cholesterol : cholesterol will be esterified by lecithin (cholesterol acyl transferase, or LCAT),then it will be transported to the core(it's not amphipathetic)3-it will be converted from nascent discoid to having a spherical shape.4-:cholesterol won't undergo degradation into CO2 to get usable form of energy in another words :we can't use cholesterol as energy source ,and the only way to get rid of it is to take it to the liver 🡪At first HDL carrying the cholesterol will bind to specific receptors on hepatocytes then pass cholesterol to liver upon binding with another receptors called scavenger receptors (SR\_B1) when liver take it up it will be converted to bile acids and it will be excreted as suchNote so any cell that turnover/die cholesterol will go from interior leaflet to the outer leaflet of the cell membrane, then it will be transported with HDL, follow the fate of HDL as we talked about earlierNote :scavenger receptors (SR\_B1) doesn't undergo down regulation ,but can be up regulated when cholesterol is needed, we find it on many cell types and hepatocytes (liver cells) are includedNote :entry of the whole particle to the hepatocyte isn't necessary ,it will interact with another particles instead , with the result that it will exchange components it's Note: we talked about esterification of cholesterol , during this process HDL will transform from HDL3 (relatively low levels of cholesterol) into HDL2 (cholesterol rich particle), when binding with HDL receptors it will be transformed into HDL3 again. Conclusion: it's good to have elevated levels of HDL cholesterol because it will be converted eventually to bile acids by liver. | 1-pass through capillaries that contain apolipoprotein lipase 2-the enzyme will convert TAG into glycerol and fatty acids 3-VLDL is converted into IDL(smaller size and higher density)4-some is taken as IDL, and some is converted into LDL that contains only ApoB100Then they bind receptors and taken up by tissues through endocytosis5-rate of synthesis of receptors decrease upon over supplement of cholesterol(to make sure that LDL isn't taken up too much by endocytosis) 6-when LDL accumulates another type of receptors will interfere(look at the note after the table) | 1-When it's transported to lymphatic system then to blood it takes apolipoprotein C2 and apolipoprotein E from HDL2-now they are ready to be transported to capillaries 3-apolipoprotein lipase will act on TAG and produce glycerol and fatty acids 4-Chylomicrons now are converted to smaller particles(remnants) and then it's taken by endocytosis to liver (Apo E helps in the endocytosis)5-Apolipoprotein C2 is returned back to HDL |

**Note**: we have another type of receptors beside LDL receptors and they are called macrophage scavenger receptors, these receptors are found on the surface of macrophages and they are non-specific meaning they can bind with wide variety of substances including modified or damaged LDL (the damage could be oxidative) the resulting LDL is no longer able to bind with normal LDL receptors however macrophage scavenger receptors can. These receptors do not undergo down regulation even when there is high uptake of modified/damaged LDL, there is no regulatory mechanism to reduce the number of receptors, this will form what is known as foam cells (they are called so based on their appearance upon staining because they contain high LDL), foam cells will accumulate in subendothelial space which will lead to attraction of more macrophages🡪 this is an indication for early atherosclerosis.

**🡪**As we said in the paragraph the damage could be oxidative this is done by the action of super oxide, nitric oxide ,hydrogen peroxide and other oxidants), these oxidants are antagonized by : vitE, vitC (ascorbic acid) or by beta carotid or other oxidants.

As a conclusion what we must know is that there is a relationship between high conc. of LDL and atherosclerosis which is when LDL accumulates meaning it's found at high conc. in blood this will lead to its oxidization taken up by macrophages leading to development of atherosclerosis.

* **CORONORY ARTERY DISEASE (ATHEROSCLEROSIS)**

**IT'S A CHOLESTEROL RELATED DISEASE**

🡪**Risk factors for this disease are either:**

**A-modifiable (changeable/controllable):**

1-cigarette smoking🡪we can quit smoking

2-obesity

3-physical inactivity

4-kidney disease

5-diabetes mellitus

6-alcohol consumption

7-stress

8-hypertension

9-elevated LDL, reduced HDL

B-non-modifiable

1. being a male>45 year
2. being a female>55 years
3. family history of CAD (coronary artery disease)

**Note:** Based on the number of risk factors we determine the suitable accepted LDL for that individual for example we might accept this LDL for a patient who is male and 40 years old but for another patient who is male but above 45 and smokes or obese it'll be considered high and we give him medications .

**CLINICAL TESTS**

We measure the whole amount of cholesterol

We measure HDL/LDL to decide the chances of having CAD:

1-Elevated levels of HDL, as we said, means more vehicles to get rid of cholesterol (to the liver), we call it good cholesterol

2-LDL causes disease (foam cells story that we've already mentioned)

**TREATMENT**

Drugs will control elevated levels of LDL.

* **Familial hypercholesterolemia:**

We must mention before talking about disease, that normal level of cholesterol is 200 mg/dl

Here, we have elevated levels of cholesterol due to absence of receptors or having abnormal ones (doesn't bind, abnormal endocytosis)

This happens by increased levels of IDL (not taken by endoctosis), they will be converted into LDL, LDL is subjected to damage in the plasma, and they will be taken by macrophages leading to cholesterol deposition in tissues, atherosclerosis, and early death in childhood

This disease has two cases, both must be treated

|  |  |
| --- | --- |
| Type2:heterozygot | Type1:homozygote |
| 1-one parent, levels of cholesterol : 300 mg/dl | 1- from both parents ,levels of cholesterol : 680-700 mg/dl |
| 2-Almost half of the receptors are missing(one gene is still functioning and the other is damaged) | 2-No receptors at all (Both genes are damaged) |
| 3-may live to 30's or 40's | 3-myocardial infarction which is fatal before age of 24 |

* EICOSANOIDS

-Eicosa: means 20

-They are called so because they are produced in the body from fatty acids with 20 carbons

-The most common 20 carbon fatty acid used: arachidonic acid, however it's not the only fatty acid used.

-They are very potent, we find them in low concentrations and a very short half life (rapid degradation) they are synthesized and released when we need them (not stored)

-They are subdivided into several classes of signal molecules:

A-prostaglandins:

1-first one discovered , they are called so because they were first discovered in prostate secretion , they used to think only males produce it because of that, but in fact females can make it too because it's produced from almost all tissues.

2-they are responsible of wide range of responses (most of them are related to inflammation , allergy reactions)

3-They are considered local hormones because they are produced locally and function on nearby cells.

B-Thromboxanes.

C-Leukotrienes.

**Functions of eicosanoids: Check slide 3**

-the most important thing to memorize:

1-they are related to smooth muscles contractions, vasoconstriction, bronchoconstriction, inflammation in general (platelets, lymphocytes) and allergy.

2-some of them have similar effect, others have just opposite effect.

3-they have wide variety of responses.

How to distinguish between them according to their structure:

arachidonic acid has 20 carbons and 4 double bonds and a carboxyl group, now most of eicosanoids are produced from arachidonic acid

🡪 Prostaglandins: five membered ring (5 carbons) and the rest 15 carbons (they form 2 side chains one having 7 and another with 8),

🡪Thromboxanes: six membered ring (5 carbons and one angle is oxygen atom) and the rest 15 carbons (they form 2 side chains one with 7 carbons and another with 8)

🡪Leukotriene: doesn't contain a ring

Leuko/tri/enes

Tri: three/Enes: double bonds

Three conjugated double bonds, conjugated means alternation between double and single. Note: in fatty acids they are non-conjugated

**Note:** rings have functional groups (hydroxyl,ketone,etc ) , they make different classes, for example cyclic pentane's functional groups of prostaglandin determine different classes of PG(B,E,G,H,I,…)

**Naming Prostaglandins:** number comes from number of double bonds in the linear portion, they will determine subclass: 1 or 2 or 3, and the letter comes from the functional group of the cyclic pentane (as we said)

**Synthesis of Eicosanoids**

-We already mentioned that they are synthesized from arachidonic acid ( arachidonic acid comes from elongation and unsaturation of **linoleic acid**),arachidonic acid is incorporated into the phospholipids , most times it's located on position two of phospholipid.

**-Phspholipase A2** works on membrane phospholipid that will liberate arachidonic acid it's is activated by chemical signals that comes to the membrane it works on position 2 itself), it's considered rate limiting step in PG synthesis.

-Note: we already said that eicosanoids are not stored, so as soon as arachidonic acid is released it will be converted to different eicosanoids

-enzymes(***cyclo oxygenase complex***) will act on arachidonic acid to convert it to PGg then directly to PGh, then from PGh2 we can produce both PGs and thrombaxanes

-PGh2 is considered as the parent compound of all PG and thromboxanes

🡪 Different PG synthases in different cells/tissues will produce different classes of PG from the same molecule (PGh2)

-BUT, leukotrienes are made from **direct** conversion of arachidonic acid without the involvement of PG

-we have other substances, signal molecules that are called HydroxyEicosaTetraEnoic acid (HETE)

-we talked earlier about cyclo/oxygnase complex (common name COX) which is named so because it introduces oxygen to the compound in addition to cyclic ring formation, as a conclusion this complex has two components : cyclo oxgynase and peroxidase( the last one converts peroxide on carbon number 15 into hydroxyl)

**Eicosanoids can be synthesized from other poly unsaturated F.A (not always arachidonic) this explains the numbers in the PG names**

**-**common precursor: arachidonic acid :EicosaTetraEnoicAcid Four double bonds, it will give us eicosanoids with 2 double bonds (2 double bonds in linear portion, and 2 for ring is formation)

-EicosaPentaEnoicAcidFive double bonds, it will give us eicosanoids of the 3 double bonds in linear portions (2 goes for the ring formation, 3 for linear chain)

-EicosaTriEnoicAcidThree double bonds, it will give us eicosanoids of the one double bonds in the linear portion (2 will be taken for ring formation, the one left for linear portion)

-What is the significance of all this? Variety of function formed by all these classes, specially between thromboxane 2 and 3 (2 will lead to platelets aggregation and 3 will do the opposite) with the result that thromboxane 3 will protect against atherosclerosis because one of manifestation of atherosclerosis is platelets aggregation which will form thrombi, so decreasing aggregation will protect against myocardial infarction.

-we must eat eicosapentaenoicacid sources, they will lead to synthesis of 3 series eicosanoids, thromboxane 3 is one of them, it's classified as omega 3 and sea food is rich in omega 3.

**Inhibition of PG synthesis:**

1-steriodal anti-inflammatory such as cortisone (eye infections and joint infections treatment, immunity related inflammations)

How they inhibit PG synthesis?? They inhibit phspholipase A2, decreasing release of arachidonic acid, decreasing rate of PG, which are related to inflammation

2-non-steroidal anti-inflammatory such as aspirin (acetylsalicylate)

It will cause acytylation of cyclo oxygnase (on serine on the active site of this enzyme) making it inactive, sometimes by irreversible binding to this enzyme, it will inhibit platelet aggregation, it's given in very low dose (80 mg) to inhibit enzymes produced by platelets, small amounts are sufficient because platelets are inable to synthesis the inhibited enzyme due to the absence of the nucleus and protein synthesis.

**Cyclo oxgynase exist in two forms:**

-Cyclo oxgynase 1: it's constitutive (found constant at the same level in the cell), **unlike** cyclo oxgynase 2 it's inducible (produced due to inflammation signals in monocytes, macrophages, smooth muscles)

Cyclo oxygnase 1: is found in gastric mucosa, kidney, platelet functions

Inhibitors exist in two forms: non-selective: you inhibit both forms of cyclo oxgynase, so if you want to decrease inflammation you will end up affecting gastric mucosa.

Selective cyclo oxgynase2 inhibitors: will inhibit cyclo oxygnase 2 only, that will prevent inflammation in this way we are preventing side effects happening if we inhibit cyclooxgynase 1 as well.

 (e.g: asprin is not selective and it will hurt stomach because cyclo oxgynase 1 which exists in the gastric mucosa will be inhibited as well)

Note: there's no such a thing as selective cyclo oxgynase 1 inhibitor

 