Biochemistry Team 435

LIPOPROTEINS

LECTURES SUMMARY

Lipoproteins

Why we need them?	To transport lipid compounds in plasma (aqueous environment) since lipids are relatively water insoluble			
Clinical problems related to lipoproteins	Atherosclerosis and hypertension	Coronary heart diseases	Hyperlipoproteinemias & Hyporlipoproteinemias	Fatty liver

Structure	**Outer coat:**	**Inner coat:**	
	1. Apoproteins Or apolipoprotein Classes are abbreviated as: Apo-A, B, C, D, E Function: ▪ Structural and transport function ▪ Enzymatic function ▪ Ligands for receptors	1. Triacylglycerols (TG)	• According to the type of lipoproteins • Different lipid components in various combinations
	2. Phospholipids	2. Cholesterol ester (CE)	
	3. Cholesterol (Unesterified)		

Types of lipoproteins	Main transporting form for	Facts
Chylomicrons	TG of dietary origin	• Assembled in intestinal mucosal cells • Carry dietary lipids to peripheral tissues • Lowest density & Largest size • Highest % of lipids and lowest % proteins • Responsible for physiological milky appearance of plasma
Very low density Lipoprotein (VLDL)	TG of endogenous (hepatic) synthesis	• Assembled in liver • Carry lipids from liver to peripheral tissues • Nascent VLDL: contains Apo B-100 • Mature VLDL: Apo B-100 plus Apo C-II and Apo E (from HDL) • End product is IDL and LDL
Low density Lipoprotein (LDL)	Free cholesterol	-
High density Lipoprotein (HDL)	Esterified cholesterol	

Diseases related to VLDL

Hypolipoproteinemia	Abetalipoproteinemia	• Defect in TG-transfer protein • Apo B-100 cannot be loaded with lipid • Accumulation of TG in liver
Hyperlipoproteinemias	Type I hyperlipoproteinemia	• Familial Lipoprotein lipase deficiency • Due to deficiency of lipoprotein lipase or its cofactor (Apo C-II) • Shows a dramatic accumulation (≥1000 mg/dl) of chylomicrons in plasma • Usually associated with acute abdomen due to acute pancreatitis • ↑ plasma TG even in the fasted state
	Familial type III hyperlipoproteinemia	• (Familial dysbetalipoproteinemia) • due to Apo E deficiency • Associated with hypercholesterolemia & premature atherosclerosis
Fatty Liver (hepatic steatosis)	• Imbalance between hepatic synthesis of TG and secretion of VLDLs. • Accumulation of TG in liver	

Lipoprotein lipase

What is it?	Extracellular enzyme, anchored by heparan sulfate to the capillary walls of most tissues
Site	• Adipose tissue • Cardiac & skeletal muscle
Facts	• Requires ApoC-II for activation • Degrades TG into glycerol and free fatty acids • Insulin stimulates its synthesis and transfer to the luminal surface of the capillary • If deficient (or if apo C-II is deficient) → type 1 hyperlipoproteinemia = familial lipoprotein lipase deficiency)
Importance	Modifications of Circulating VLDLs How? 1- Degradation of TG by lipoprotein lipase → VLDLs become Smaller in size More dense 2- Apo C & Apo E return back to HDL 3- Some TG are transferred from VLDL to HDL in exchange with cholesterol ester (By cholesterol ester transfer protein) VLDL → IDL (returns Apo E to HDL) → LDL

Lipoproteins	Low density lipoprotein (LDL)	High density lipoprotein (HDL)
Composition	Mostly free cholesterol	▪ Mostly cholesterol ester ▪ More % protein ▪ More % phospholipids
Function	Transport cholesterol from liver to peripheral tissues	• Reservoir of apoproteins e.g., Apo C-II and E to VLDL • Uptake of cholesterol From other lipoproteins & cell membranes (HDL is suitable for uptake of cholesterol because of high content of PC that can both solublizes cholesterol and acts as a source of fatty acid for cholesterol esterification) • Esterification of cholesterol Enzyme: PCAT/LCAT Activator: Apo A-I Substrate: Cholesterol Co-substrate: PC Product: Cholesterol ester (& Lyso-PC) • Reverse cholesterol transport
Production	Produced in the circulation as the end product of VLDLs. - Compared to VLDLs, LDLs are: ▪ Smaller size and more dense ▪ It contains only apo B-100 ▪ Less TG More cholesterol & cholesterol ester	Produced by intestine and liver • Nascent HDL: Disk-shaped Contains apo A-I, C-II and E Contains primarily phospholipid (PC) • Mature HDL (HDL2): First, the HDL3 collects cholesterol (C) Then, C is converted to CE (C- ester) The HDL2 is the spherical mature particle
Transport steps	1) Uptake of LDL at tissue level by LDL receptor mediated endocytosis 2) Recognized by apo B-100 3) Release of cholesterol inside the cells for (Utilization - Storage as cholesterol ester – Excretion) 4) Degradation of LDL: into amino acids, phospholipids and fatty acids 5) Degradation or recycling of receptor	1) Efflux of cholesterol from peripheral tissues and other lipoproteins to HDL3 2) Esterification of cholesterol & binding of HDL2 to liver and steroidogenic cells by scavenger receptor class B (SR-B1) 3) Selective transfer of cholesterol ester into these cells 4) Release of lipid-depleted HDL3 This is called → Reverse cholesterol transport This is what makes HDL levels in reversed relation with atherosclerosis
Regulation of LDL Receptor - Mediated Endocytosis	Down regulation	High intracellular cholesterol content → ▪ Degradation of LDL receptors ▪ Inhibition of recepotor synthesis at gene level ▪ Decrease No. of receptor at cell surface ▪ Decrease further uptake of LDL ▪ Decrease de novo synthesis of cholesterol
	Up regulation	Low intracellular cholesterol content → ▪ Recycling of LDL receptors ▪ Stimulation of receptor synthesis at gene level ▪ Increase No. of receptor at cell surface Increase further uptake of LDL ▪ Increase de novo synthesis of cholesterol

Atherosclerosis

What is it?	Imbalance in "cholesterol homeostasis" results in: 1. Cholesterol deposition in the wall of blood vessels 2. Thickening of the wall 3. Narrowing of the lumen → eventually "Atherosclerosis"
How is "cholesterol homeostasis" maintained?	By the balance between a. Cholesterol transport from liver to peripheral tissues by LDL (bad cholesterol carrier) b. Reverse cholesterol transport from peripheral tissues to liver by HDL (good cholesterol carrier)
Pathogenesis	Modified (oxidized) LDL → Oxidative stress → uptake by macrophage scavenger receptor, which is: • Scavenger receptor class A (SR-A) • Low-affinity non-specific receptor • Un-regulated receptor Macrophage transformation into → Foam cell → Atherosclerotic plaque formation
Laboratory Investigation of Atherosclerosis	◊ Serum lipid profile: 10-12 hours (O/N) fasting Measurement of: ▪ Serum triglyceride level (reflect chylomicron and VLDL levels) ▪ Serum total cholesterol level (reflect LDL and HDL levels) ▪ Serum HDL-cholesterol level ▪ Serum LDL-cholesterol level ◊ Others, Serum lipoprotein electrophoresis Serum apoprotein levels e.g., apo-B
LDL-related disease & relation with atherosclerosis	**Hyperlipoproteinemia → Type II- a Hyperlipoproteinemia** • Functional defect of LDL-receptor • Increase plasma LDL level & therefore, plasma cholesterol level • Pre-mature atherosclerosis and increased risk for early-onset ischemic heart diseases • Associated with the presence of tendon xanthomas on hands and ankles