Lipids – digestion and absorption, blood plasma lipids, lipoproteins

Biochemistry II
Lecture 1

2009 (J.S.)

Lipids in the diet

Western diet contains **40 % of lipids or more**.

From that amount, approx. **90 % triacylglycerols,**

low amounts of phospholipids, esterified and free cholesterol, glycolipids, and lipophilic vitamins.

Lipids – triacylglycerols (as well as free fatty acids and both free and esterified cholesterol) are **very hydrophobic** – they are not soluble in water unless they are, in the presence of **natural tensides** emulsified and/or included in micelles.

Digestion of lipids

In the mouth and stomach, a negligable amount of triacylglycerol may be hydrolysed by the action of **lingual** and **gastric lipase**, particularly in sucklings.

Mechanical action of the stomach converts dietary lipids into an emulsion containing droplets about 1 μm in diameter.

In the small intestine,

hydrogen carbonate secreted by pancreas raise pH to the value ~ 6. In the presence of **bile acids**, fat droplets form **mixed micelles** (< 20 nm). The protein **colipase**, secreted along with lipase, binds to the dietary fat and to the lipase (1:1) causing it to be more active.

Pancreatic lipase hydrolyzes fatty acids from positions 1 and 3 of triacylglycerols, producing free **fatty acids and 2-monoacylglycerols**.

The pancreatic secretion also contains **cholesterol esterase** that remove fatty acids from cholesterol esters and **phospholipases** that digest phospholipids to their components.

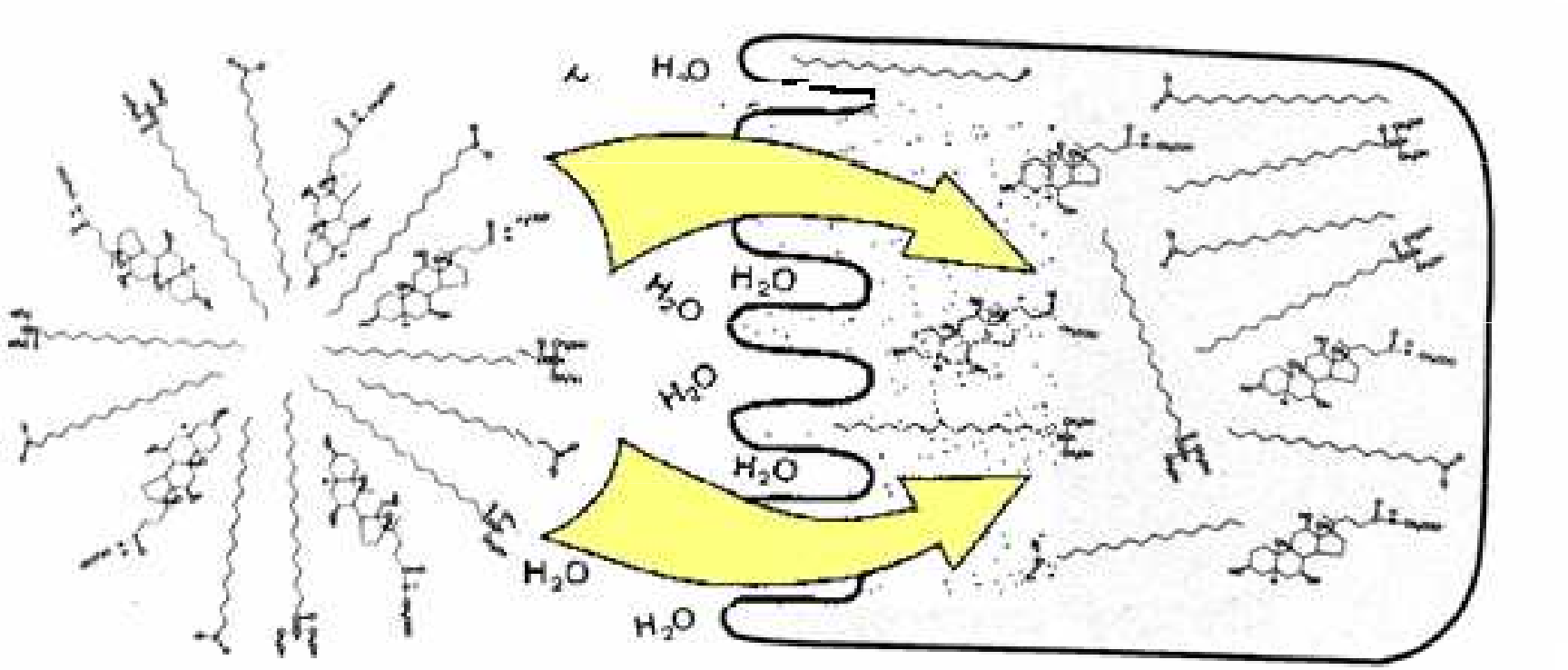
Lipid absorption through the brush border microvilli of the enterocytes lining the lumen is either **preceded by dissociation** of the micelles or **the micelles enter the cell by a channel** (protein NPC1L1).

Short and medium chain fatty acids (C_4 to C_{12}) don't require bile acids for their absorption.

The **bile acids**, which remain in the intestine, are extensively absorbed when they reach the ileum.

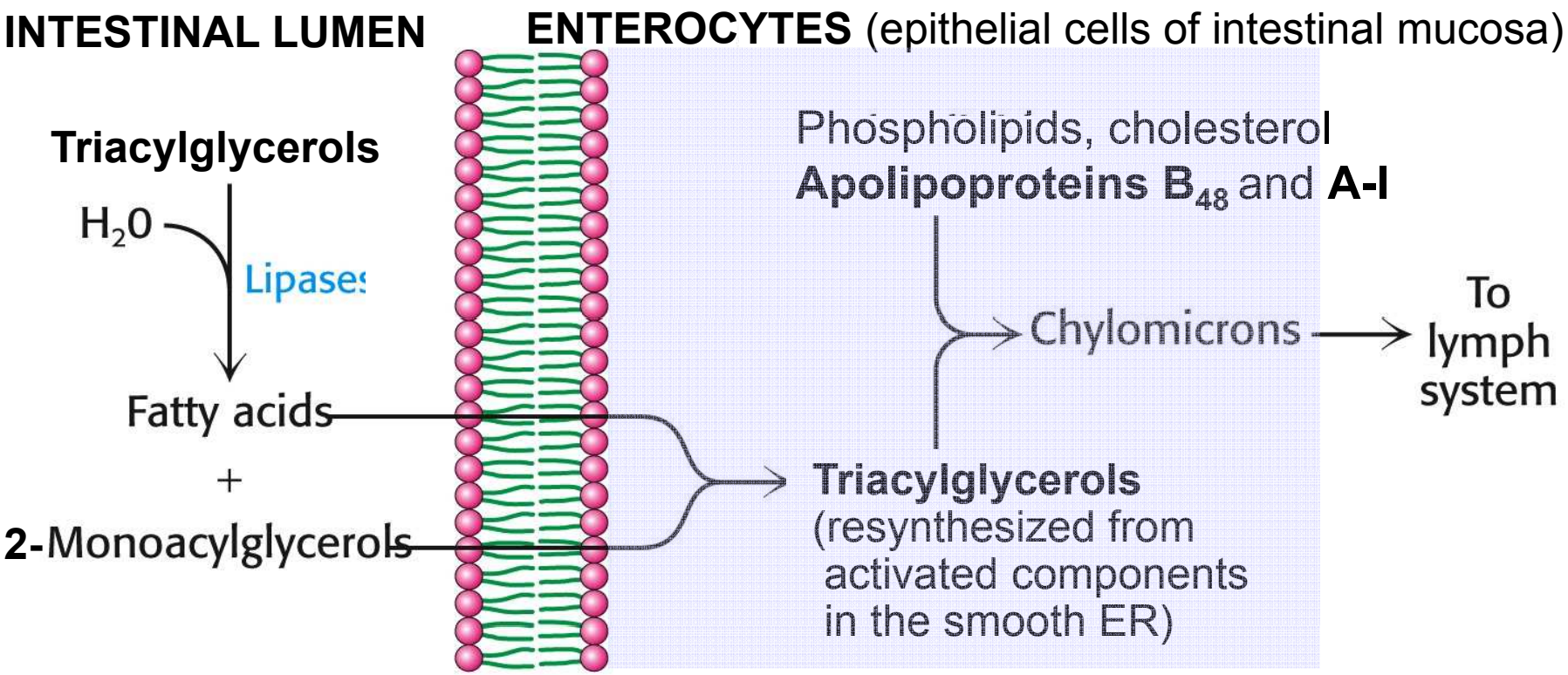
The mixed micelles

in the chyme are composed, in varying proportions, of the fatty acids (FFA), mono- and diacylglycerols (MG and DG), perharps some unhydrolysed triacylglycerol (TG), and anions of bile acids, together with minor components of the diet such as phospholipids, free cholesterol, and fat-soluble vitamins.



Intestinal lumen **Mucosal cell (enterocyte)**

Within the mucosal cells, triacylglycerols are resynthesized (the details are given in Biochemistry I – Metabolism of lipids



Chylomicrons secreted (exocytosis) from the mucosal cells enter the chyle of **the lymphatic lacteals**. Thoracic duct delivers chylomicrons into the blood.

Short-chain fatty acids glycerol may enter the branches of the portal vein and are transported to the liver bound to plasma albumin..

Plasma lipids

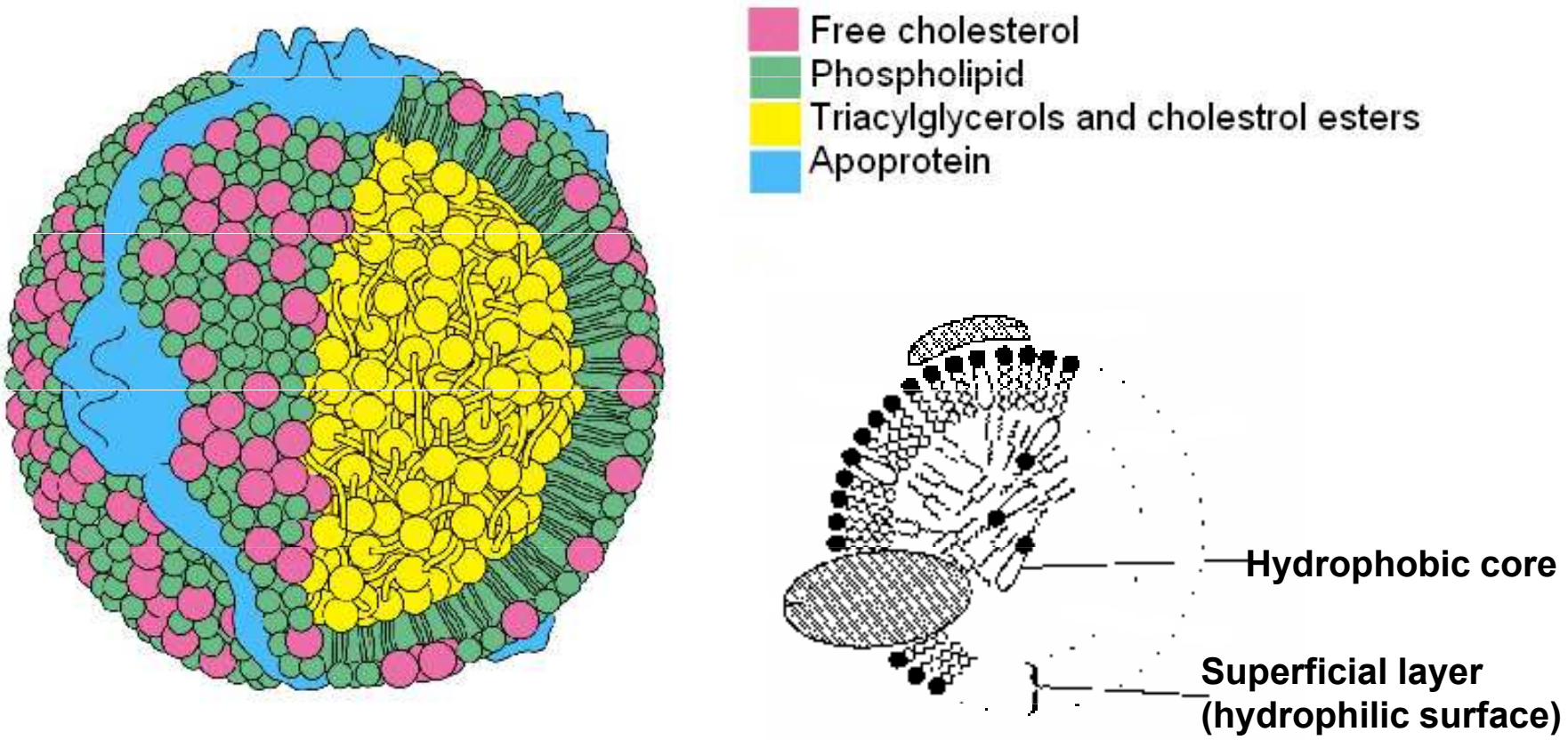
Total concentrations of different lipid classes:

	Approx. M_r	Approx. median value of ***c***	Recommended cut-off point	Mole fraction of total FA	Approx. mass concn. ρ
Triacylglycerols	860	**1.5 mmol/l**	2.3 mmol/l	0.35	1.3 g/l
(Phospholipids)	750	(2,5 mmol/l)	–	0.30	(2.0 g/l)
Cholesterol, total	385	**5.0 mmol/l**	desirable < 5.2 mmol/l (high risk > 6.2 mmol/l)	0.30	2.0 g/l
Non-esterified FA	260	0.5 mmol/l	–	0.05	0.1 g/l

Average mass concentration of all lipids approx. **5 g l^{-1}** .

Lipoprotein particles transport triacylglycerols and cholesterol in body fluids

Common structure of lipoprotein particles:



E.g. the diameter of a low-density lipoprotein (**LDL**) particle is about 30 nm and it consists of about **50 % cholesterol** (both free and esterified), 20 % phospholipids, 20 % apoprotein B-100 and 10 % triacylglycerols.

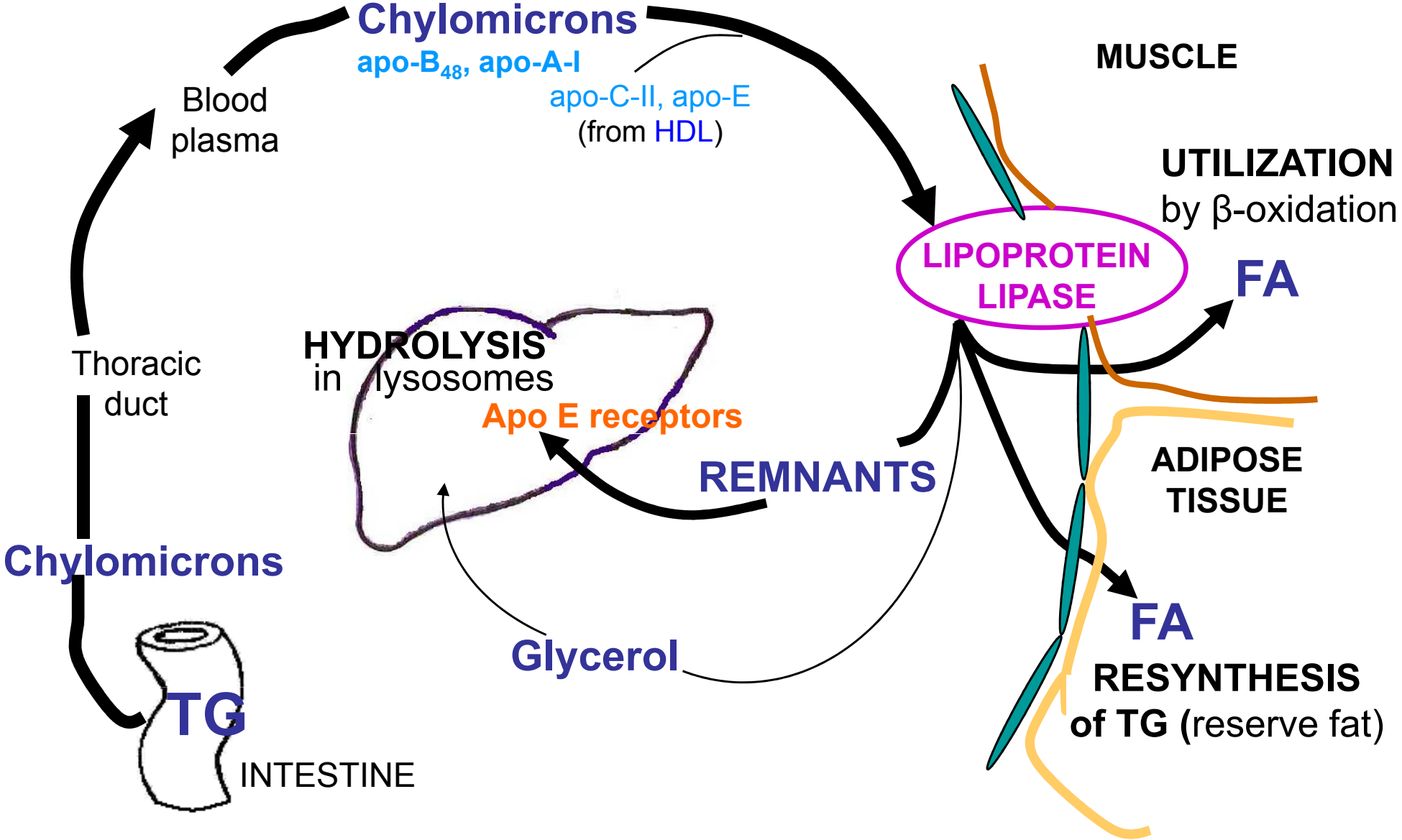
Plasma lipoproteins

	Density	Size nm	Elpho mobility	Origin	Protein %	TG %	C + CE %	PL %
Chylomicrons	**< 950**	100-1000	none	Intestinal mucosa	1 – 2 B_{48}, A-I	**> 85**	3-7	7
VLDL	950-1010	30-90	**pre-β**	Liver (intestine)	< 10 B_{100}, C-II, E	**~ 60**	~ 15	15
IDL	1005-1020	25-30		(VLDL)	11 B_{100}, E	~ 30	~ 40	~ 20
LDL	1020-1063	20-35	**β**	(IDL)	20 B_{100}	~ 10	**~ 50**	20
HDL nascent	1125-**1210**	3.6-4.4		Liver (intestine)	**~ 50**			
spherical **HDL_3** **HDL_2** (CE-rich) **HDL_2** (TG-rich)	1063-1125	4.4-6.3	**α**		A-I, A-II A-I (C, E)	~ 3 (< 3) (> 3)	**~ 25** (> 25) (< 25)	~ 25

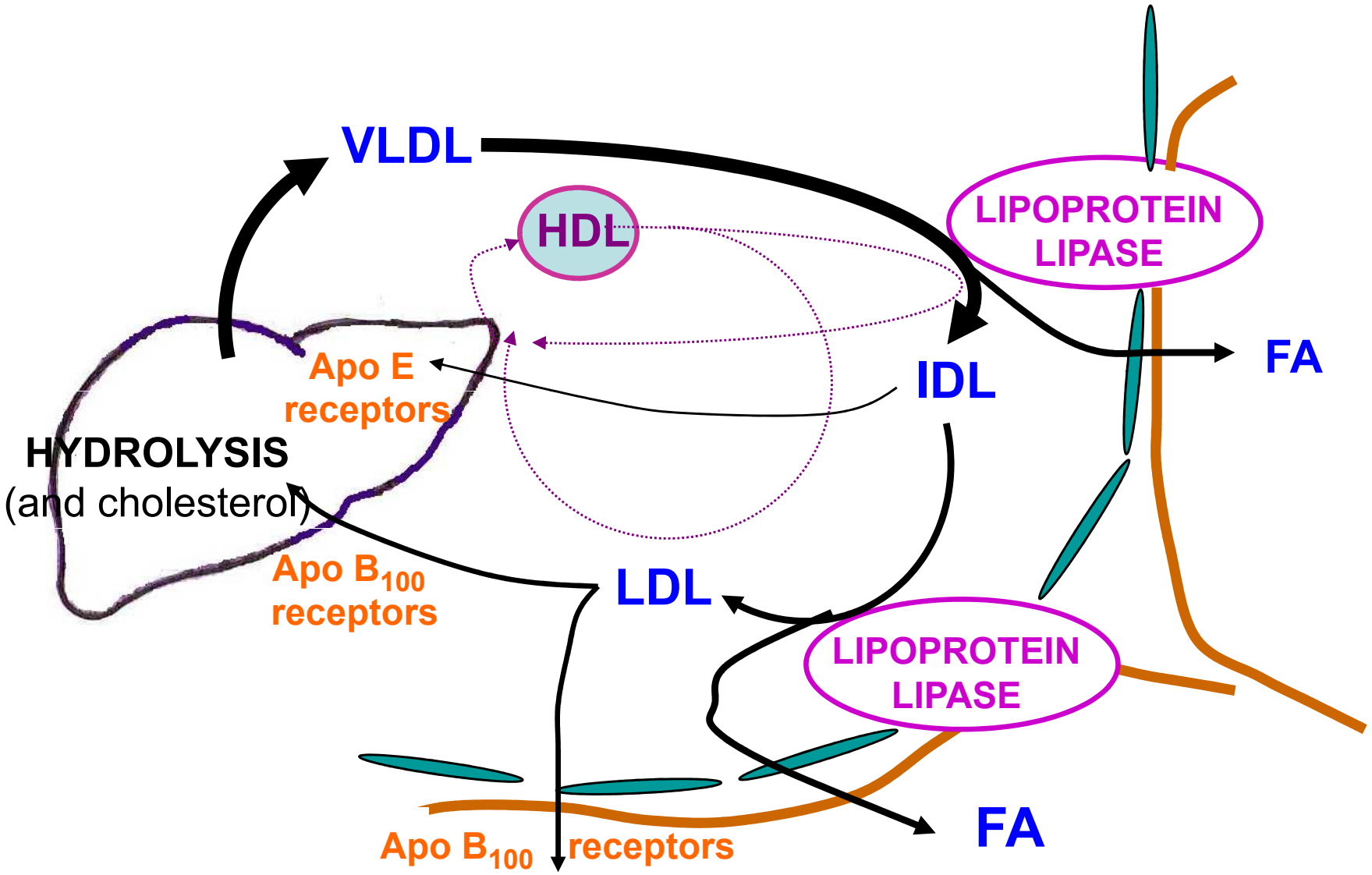
Major plasma lipoproteins and their functions

	M_r	Mean plasma level mg / l	Constituent of	Function
Apo A-I	28 330	1 210	**HDL and CM** (risk of high II/I ratio)	**LCAT activation**
Apo A-II	17 380	370		LCAT inhibition (displaces the enzyme from lipoprotein)
Apo B_{100}	550 000	950	**VLDL, IDL, LDL**	recognition of LDL
Apo B_{48}	270 000	..	**CM**	recognition of chylomicrons
Apo C-I	6 610	70	**VLDL, HDL**	**LCAT activation**, LPL inhibition
Apo C-II	8 800	40	**HDL, VLDL, CM**	**LPL activation** (cofactor)
Apo C-III	8 750	130	**VLDL, CM, HDL**	LPL inhibition
Apo E_2 **Apo E_3**	~ 34 000	~ 50	**nascent HDL** **HDL → CM, VLDL**	recognition of CM, IDL (HDL?) polymorphic forms
(Apo E_4)	high levels in coronary heart disease and Alzheimer disease			

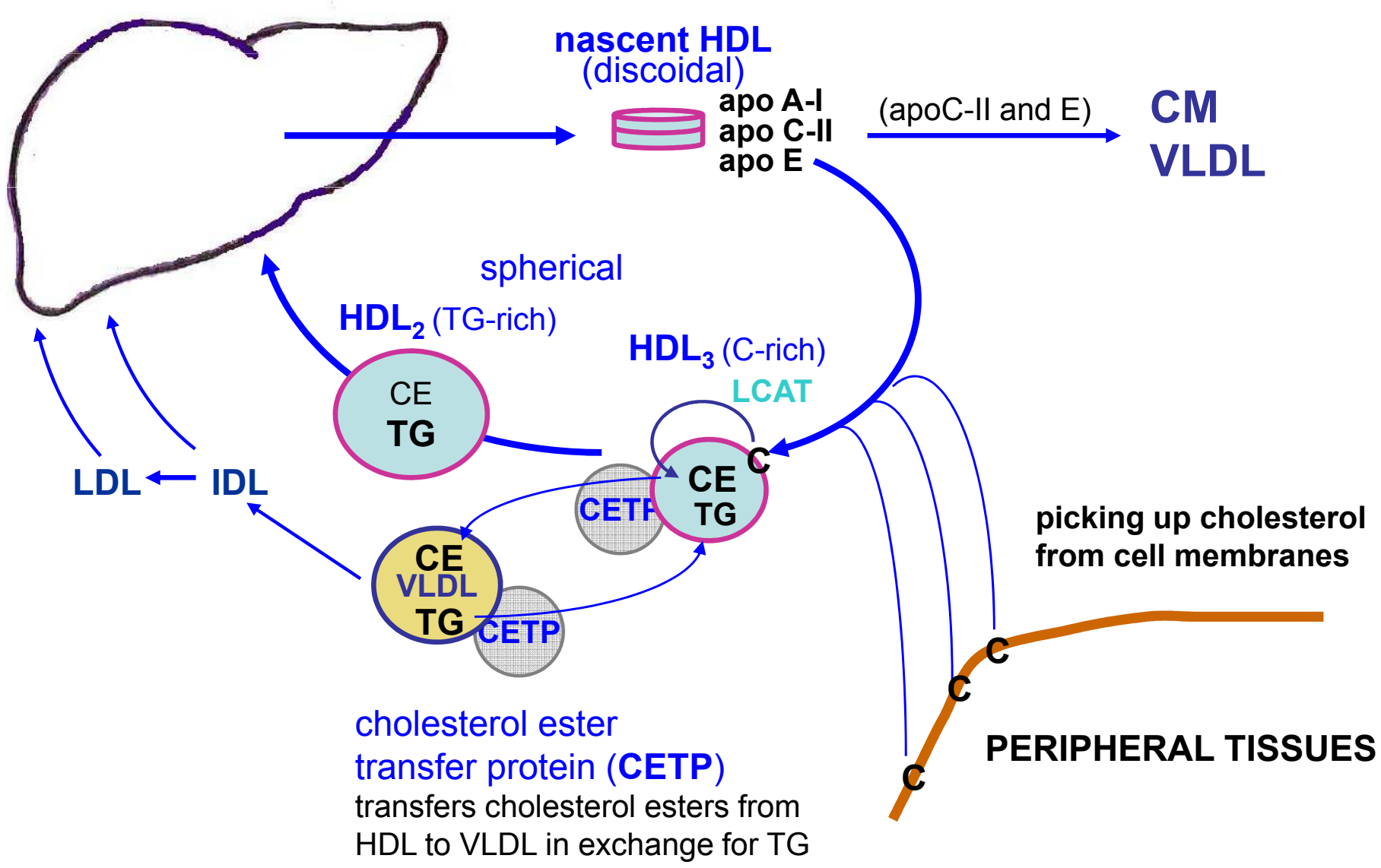
Transport of exogenous lipids (dietary fat)



Transport of endogenously synthesized lipids

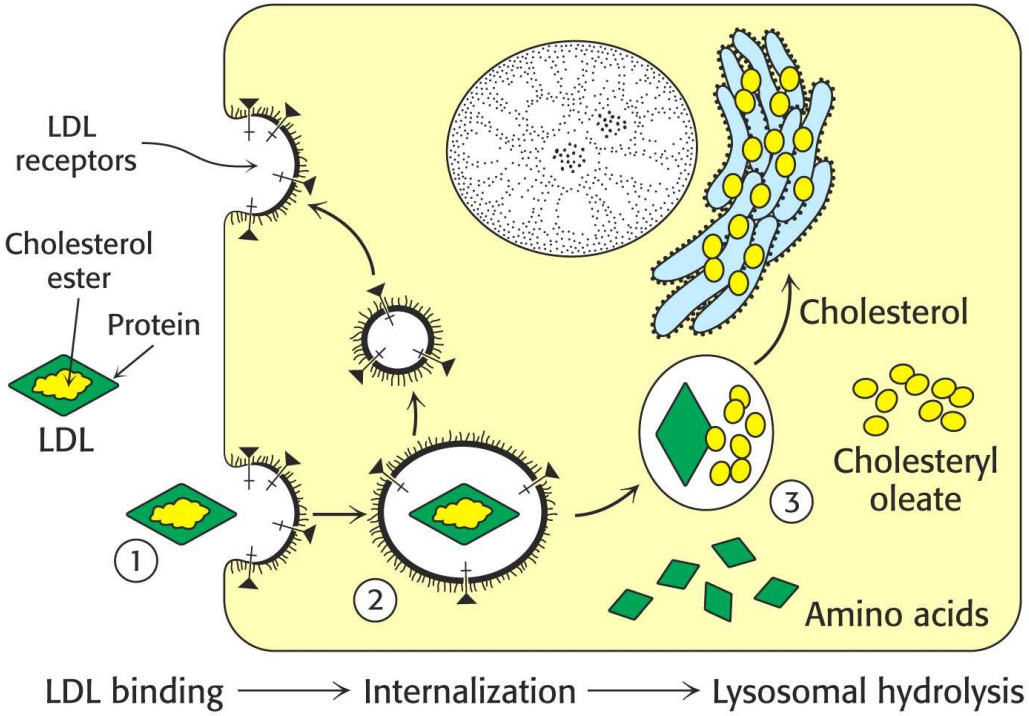


Function of HDL



Cellular uptake of LDL

Apo B_{100}/E receptor-mediated endocytosis of intact LDL:



Cholesterol that enters the liver cell this highly specific way **inhibits *de novo* cholesterol synthesis** as well as synthesis of new LDL (apo B_{100}) receptors. (Goldstein and Brown)

Cholesterol uptake (namely from chemically modified LDL) by scavenger receptors of macrophages and other types of cells **does not regulate** intracellular cholesterol levels, but it may result in formation of foam cells or initiate apoptosis.

Scavenger receptors

internalize **modified LDL** (oxidized or Tyr-nitroLDL).

While the expression of apo B/E receptor is inhibited by the high intracellular concentration of cholesterol, the expression of the scavenger receptor remains unregulated (on the contrary, the expression of it is supposed to be induced).

The scavenger receptors **class A** are present on **macrophages**, scavenger receptors **class B** are on **hepatocytes and other cell types** (adipocytes, blood platelets, myocytes, endothelial cells, etc.)

It is very interesting that one of the scavenger **receptors class B**, type I, called membrane protein CD 36 or **fatty acid translocase** (FAT, identical with the glycoprotein IV/IIIb on blood platelets) **enables the transport of fatty acids, both free and esterified cholesterol, and anionic phospholipids across the plasma membrane through facilitated diffusion**.