

# Lipoproteins and lipoprotein lipase in health and disease

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Received on September 24, 1985; Revised October 28, 1986.

## Abstract

Epidemiological data have established a consistent negative correlation between cholesterol concentrations in plasma high-density lipoproteins (HDL) and incidence of coronary heart disease. It has been postulated that the protective effect may relate to a role of HDL in the removal of cholesterol from peripheral tissues. The lipoprotein classes correlate with one another, pre-beta being generally synonymous with VLDL, beta with LDL and alpha with HDL. Lipoprotein lipase is most active in the capillaries of adipose tissue, cardiac and red skeletal muscle, and the lactating mammary gland. The enzyme is synthesized within the cells of a variety of tissues and is active extracellularly at the surface of capillary endothelia. The present review is aimed to explain the current state of information concerning lipoproteins, their transport and functions and the pathophysiological significance of lipoprotein lipase (LPL).

**Key words:** Lipoproteins, cholesterol, lipoprotein lipase and lipid.

## 1. Introduction

Lipids are transported exclusively in association with specific plasma proteins. Certain polar lipids are bound predominantly to relatively small proteins such as albumin, lysolecithin or to specific binding proteins (retinol) and these lipids are transported across the vascular endothelium or its cells upon dissociation from the vehicle, presumably in molecular form or in association with cellular binding proteins. Nonpolar lipids are transported in much larger macro-molecular complexes, the plasma lipoproteins. Such nonpolar lipids (triglycerides, cholesterol esters, retinyl esters) comprise the core of the spherical plasma lipoproteins, shielded from the aqueous environment by a mixed monolayer of polar lipids (phospholipids, cholesterol) and a group of specific proteins (apolipoproteins) (fig. 1).

The lipoproteins are generally divided into four categories: chylomicrons, very low-density lipoproteins (VLDL), low-density lipoproteins (LDL) and high-density lipoproteins (HDL). The most widely used classification of lipoproteins, based on their flotation at densities of 1.063-1.21 g/ml, was introduced first of all by Gofman *et al*<sup>1</sup>. Because of their high lipid content, these particles have a lower density than other proteins in the circulation. The initial techniques employed for their isolation from plasma are ultracentrifuge flotation and electrophoretic mobility.

In addition to their transport function and the solubilization of hydrophobic lipids in the aqueous environment of blood, the protein component of lipoproteins, the

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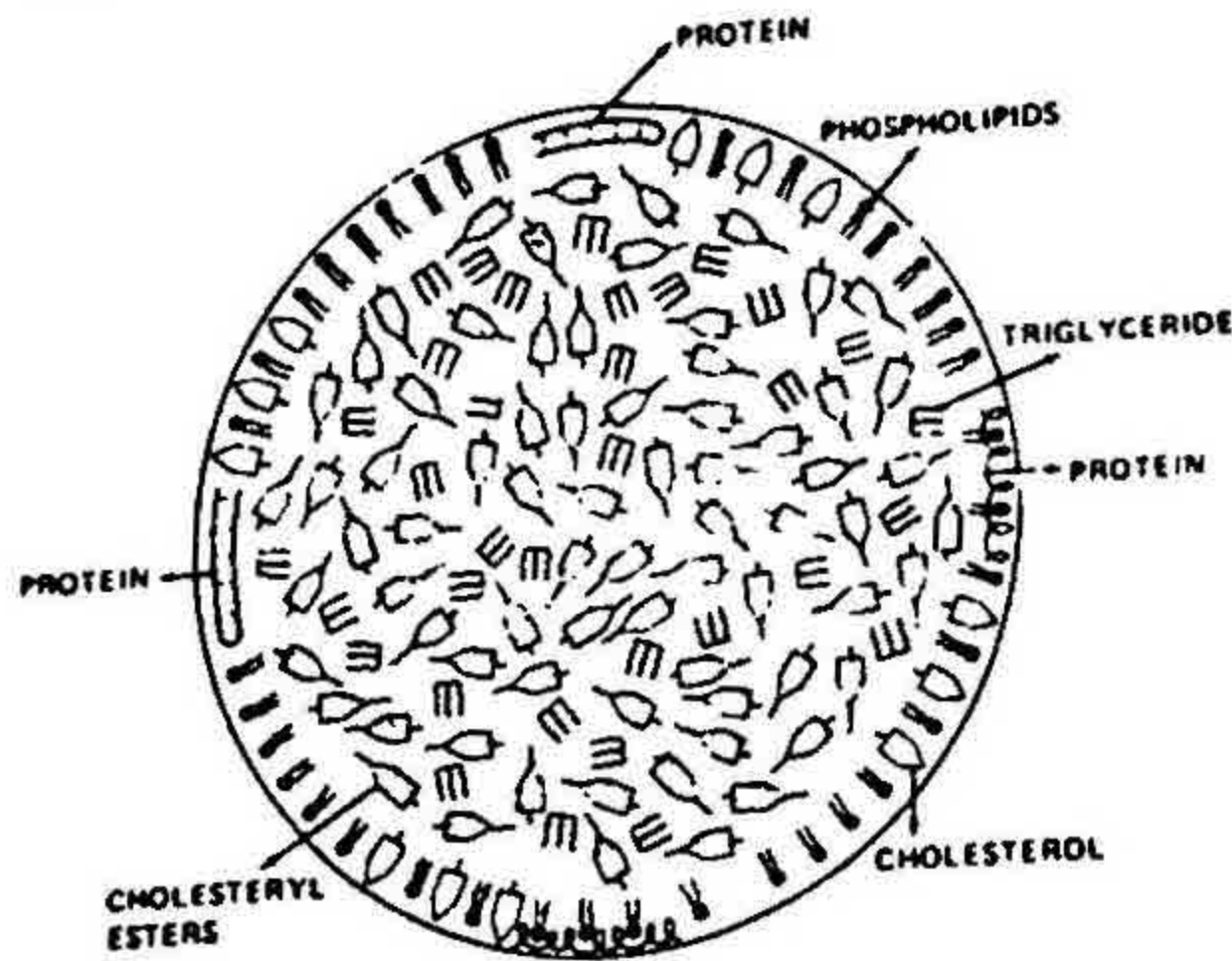


FIG. 1. A general structure for lipoproteins.

apoproteins, have important metabolic functions<sup>2, 3</sup>. There are at least seven different lipoprotein apoproteins. Some apoproteins have a primary role in lipid transport and others are specific activators of enzymes involved in lipolysis and interconversion of lipoproteins.

## 2. Lipoproteins

### 2.1. Chylomicrons

Chylomicrons have a core of triglyceride surrounded by an outer layer of phosphatidylcholine, cholesterol and apolipoproteins, that form a monomolecular layer on the surface of the particles<sup>4</sup>. Approximately 66% C-apolipoproteins (Apo CI, Apo CII and Apo CIII), 22% protein B and 12% apoprotein A are present in chylomicron apoproteins. The large size of chylomicrons is perhaps related to a need to conserve apoprotein B, which is essential for their secretion from the intestinal mucosa into the lymphatics<sup>5</sup>. Chylomicrons are the most rapidly catabolized of all the lipoproteins. The catabolism of chylomicrons proceeds in two main phases: first, the triglyceride core is markedly reduced through the action of lipoprotein lipase, an enzyme that hydrolyses lipoprotein-triglyceride at the luminal surface of the capillary endothelium<sup>6</sup>. Due to hydrolysis in extra hepatic tissues, the particles are reduced in size to cholesterol-enriched remnants that are removed by the liver. Recent evidence suggests that changes in the composition of the apoproteins on the surface of chylomicron remnants are the major determinants for hepatic recognition, a reduction in apoprotein C and an increase in apoprotein E content are prerequisites for efficient remnant uptake by the liver<sup>7</sup>.

### 2.2. Very low-density lipoproteins (VLDL)

The organization of the components of VLDL within the lipoprotein particle resembles that of chylomicrons: there is a neutral lipid core and surface film of phospholipids, cholesterol and apoproteins<sup>8</sup>. VLDL overlap with chylomicrons and with LDL at the two extremes of the density range, and are isolated from chylomicron-free plasma at densities

**Table I**  
**Properties of human serum lipoproteins**

Properties	Chylomicrons	VLDL	IDL	LDL	HDL <sub>2</sub>	HDL <sub>1</sub>
Density g/ml	< 0.96	0.96–1.006	1.006–1.019	1.109–1.063	1.063–1.125	1.125–1.210
Diameter nm	80–500	30–80	25–35	21.7	8.5–10	7.5–3.5
Molecular weight	$10^3$ – $10^4 \times 10^6$	$5$ – $27 \times 10^6$	$2.7$ – $3.5 \times 10^6$	$2.2$ – $2.7 \times 10^6$	$1.8$ – $2.6 \times 10^5$	$1.5$ – $1.8 \times 10^5$
Electrophoretic mobility in PAGE*	Origin	Pre $\beta$	Slow Pre $\beta$	$\beta$		

\*PAGE: Polyacrylamide gel electrophoresis.

less than 1.006 g/ml. The VLDL form a continuum of various sizes (30–88 nm diameter) and molecular weights ( $5$ – $30 \times 10^6$  daltons) that are a reflection of the extensive changes in composition which occur in the circulation (Table I). The size of the VLDL particles is directly related to their triglyceride content, and inversely to the levels of phospholipid and protein. Apoprotein B accounts for 20–40% of total VLDL protein<sup>9</sup>, apoprotein C for 50% and apoprotein E for 13%.

The catabolism of VLDL occurs by a stepwise reduction of the triglyceride core through the action of lipoprotein lipase, a process that, in man, leads to the formation of intermediate density lipoprotein (IDL) and ultimately of low-density lipoprotein (LDL). It is not clear whether (LDL) are delipidated at the peripheral capillary endothelium or the triglyceride is hydrolysed in the liver endothelium directly by hepatic lipase<sup>10</sup>. A precursor-product relationship has consistently been reported for the apoprotein B moiety of VLDL, LDL and IDL indicating that LDL are the end product of a series of delipidation steps of VLDL<sup>11</sup>. Nevertheless, enough evidences are forthcoming for the removal of the LDL by the liver (apo BE) receptor<sup>12</sup>.

### 2.3. Low density lipoproteins (LDL)

The main function of LDL is to transport cholesterol ester to nonhepatic tissues. Initiation to this is taken place by the interaction of plasma LDL with specific cell surface. LDL is internalized and in the further degradation lysosomal enzymes play an important role. In the process of cholesterol delivery to the cells, the protein component of LDL is hydrolysed to aminoacids, and thus the entire LDL particle is catabolised. Complete hydrolysis of apoprotein B during the transfer of cholesterol to various tissues suggests that the protein and lipid component of LDL are metabolised as one unit. Lipids comprise 75% of the mass of LDL particles and, as in the triglyceride-rich lipoproteins (Chylomicron and VLDL) form the core of the LDL particle (Table II). It is assumed that this protein (apolipoprotein B), which contains 5–9% carbohydrate, consists of a number of subunits, some of which are buried in the lipid core and others are exposed to the water surface (Table III).

**Table II**  
Composition of human serum lipoproteins lipid (Weight per cent of total lipid)

Lipoprotein	Protein (weight per cent per particle)	Triglyceride	Cholesteryl ester	Cholesterol	Phospholipid	Apoproteins major and minor
Chylomicrons	2.0	84	5.0	2.0	8.0	C (A,B,E)
VLDL	8-10	56	13.0	8.0	20.0	C,B (E)
LDL	25	10	50.0	10.0	30.0	B (C,E)
HDL	41	7.6	28.0	9.0	50.0	A (C,D,E)

**Table III**  
Function of plasma lipoproteins

Lipoprotein	Origin	Composition change (circulation)	Half life	Function
Chylomicrons	Intestine	Aquire Apo C II	5 min	TG transport
VLDL	Intestine, liver	Aquire Apo C II and CE, Aquire CE	Hours	TG transport
LDL	Circulation	From VLDL through loss of TG	Days	Cholesterol transport to tissues (anabolic)
HDL	Intestine, liver, circulation	Aquire CE	Days	Cholesterol transport from tissues to liver (catabolic), reservoir of CE, Apo C II.

CE: Cholesteryl ester, TG: Triglyceride

In support of the hypothesis that most of the LDL is degraded in extrahepatic tissues is the observation that removal of the liver does not lower the rate of catabolism of LDL<sup>13</sup>, a variety of cells in culture fibroblasts, arterial smooth muscle cells, lymphoid cells and endothelial cells are able to degrade LDL through the LDL pathway<sup>14</sup>. The essential features of the system, usually referred to as the LDL pathway are shown in fig. 2. It has been reviewed in detail by Goldstein and Brown<sup>15</sup>. Large number of receptors have been detected in cow cell membranes, the highest being in the adrenal cortex and in ovarian corpus luteum. The critical component of the LDL pathway is the specific receptor on the cell surface which binds LDL<sup>16</sup>. However, recent studies show that most LDL are catabolized in the liver. This has been demonstrated *in vivo* by the use of non-degradable LDL levels<sup>17</sup>, the presence of large amounts of LDL receptors on the liver surface using anti-LPL receptor monoclonal antibodies<sup>18</sup> and most recently by radioactive scanning techniques after injections of radioactive LDL<sup>19</sup>. The receptor appears to be a protein or glycoprotein which is probably coded by the locus at which the mutant alleles determining familial hypercholesterolemia occur. LDL receptor function has been studied by measuring the binding of <sup>125</sup>I-labelled LDL to the receptors of intact fibroblasts in

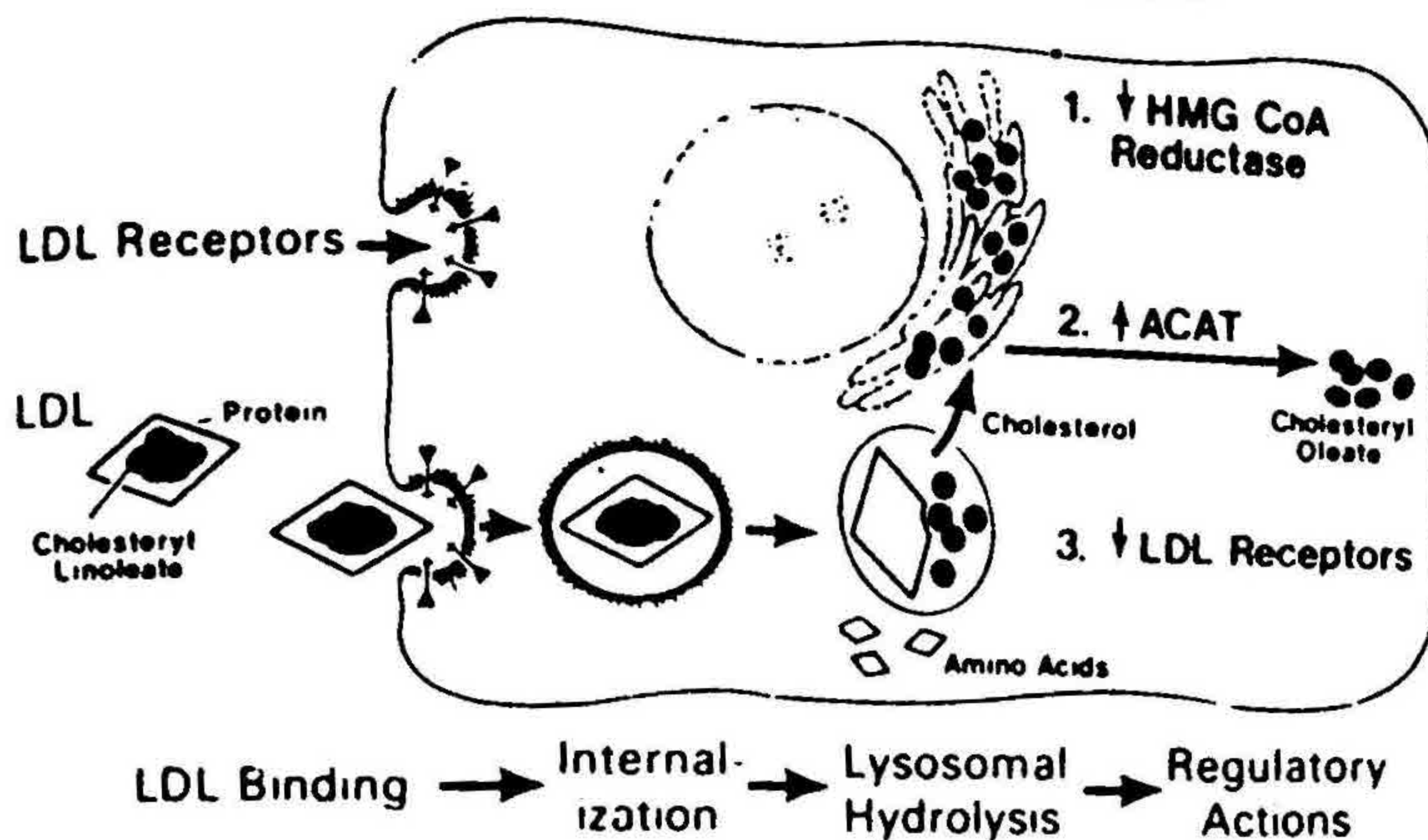


FIG. 2. Lipoprotein receptor-mediated process. LDL: Low-density lipoprotein; HMG CoA reductase: 3-hydroxy-3-methylglutaryl Co-enzyme A reductase; ACT: acyl-CoA-cholesterol acyltransferase (Reproduced with the permission of Goldstein *et al*<sup>15</sup>).

monolayer cultures. At 4°C, binding of LDL to the receptors occurs but there is no internalization<sup>15</sup>. At 37°C, however, both binding and internalization occur so the total amount of <sup>125</sup>I LDL bound to the receptor site enters the cell by internalization<sup>15</sup>. It has been shown that the spontaneous rate of dissociation of LDL bound to the receptors is very slow in comparison to the rate at which it is internalized at 37°C. Thus essentially all LDL particles that bind to the receptor are taken into the cell<sup>12</sup>.

Thus, receptor-mediated LDL uptake by the cell regulates endogenous cholesterol synthesis and also cholesterol esterification. The feedback regulation of the actual number of LDL receptors on the cell surface, which allows the cell to modulate LDL-cholesterol uptake in accordance with its needs not only for membrane cholesterol but also for the synthesis of steroid hormones, bile salt, etc. When cells are deprived of exogenous LDL the number of receptors increase progressively, reflecting an increased rate of receptor-molecule synthesis<sup>12</sup>.

#### 2.4. High density lipoproteins (HDL)

Recently, the interest on HDL has increased largely due to the strong inverse relationship between plasma levels of HDL and morbidity or mortality from cardiovascular disease<sup>20</sup>. This relationship may be the result of the special function of HDL in transport of cholesterol from peripheral tissues to the liver, thereby reducing the amount of lipid deposited in the arterial wall. The fraction produced by the intestine acquires its apoprotein C complement in the circulation from HDL, of hepatic origin; the latter is released from the liver with a full complement of apoprotein C. Nascent HDL produced by the liver has a higher proportion of apoprotein E than does plasma HDL and appears

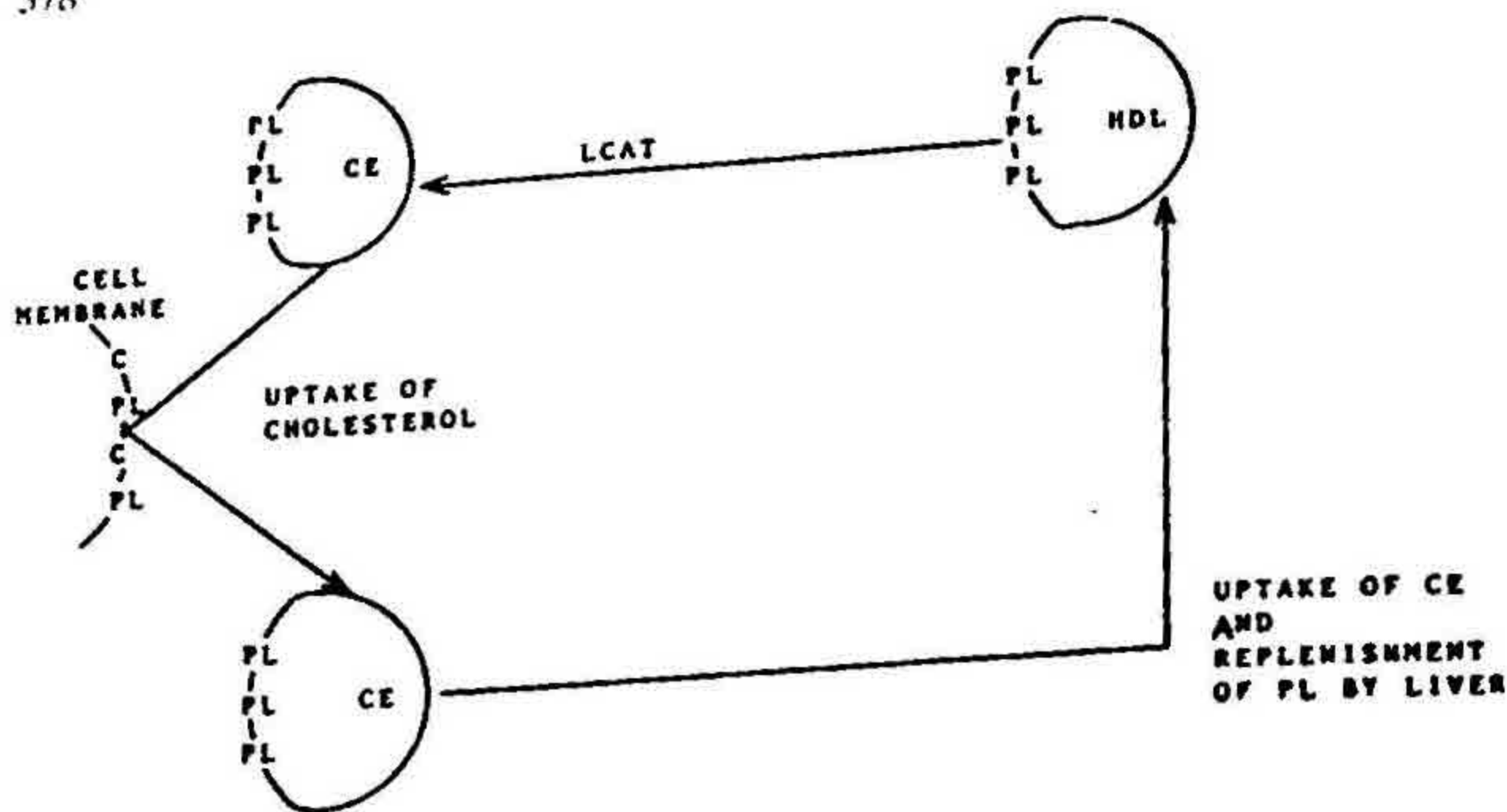


FIG. 3. Role of LCAT reaction in cholesterol transport.

as discs of about 45 nm (Table III). These particles are rich in protein, phospholipid and cholesterol, but are deficient in cholesteryl ester<sup>21-23</sup>.

The maturation of discoid HDL requires cholesterol esterification, which is mediated by the lecithin cholesterol acyl transferase (LCAT) reaction. LCAT is an enzyme, released from the liver into the circulation where it acts specifically on the plasma HDL by converting the lecithin and unesterified cholesterol of HDL to cholesteryl ester and lysolecithin<sup>24</sup>. Once esterified, the free cholesterol leaves the surface coat and moves into the nonpolar lipid core in the centre of the particle, leading to the transformation of disc-shaped 'nascent' HDL into spherical 'mature' HDL (fig. 3). It has recently been proposed that triglyceride-rich core is reduced in size by the action of lipoprotein lipase at the capillary endothelium, leaving excess surface constituents which then form bilayer folds that resemble nascent HDL. These nascent HDL discs would then acquire cholesteryl ester through the LCAT reaction and become spherical HDL particles<sup>25</sup>.

Very little is known about the catabolism of HDL. Receptor-mediated uptake by peripheral tissues and liver does not seem to occur, except in special conditions, when HDL contains apoprotein E, the specific recognition factor for lipoprotein remnant receptors. Uptake and catabolism of HDL particles involves concomitant breakdown of both lipid and apoprotein AI and AII. Some investigators have shown that uptake and catabolism of HDL apoproteins and lipids occurs separately with more uptake of cholesterol by the liver and a greater uptake of apoproteins by the kidneys<sup>26</sup>. An important function of HDL is to act as a reservoir of both apoproteins and cholesteryl ester for other circulating lipoproteins (Table II). Another function is the provision of cells with cholesterol in certain tissues in certain species<sup>27</sup>.

### 2.5. Lipoprotein lipase

Lipoprotein lipase (LPL) is the key enzyme in the catabolism of triglyceride-rich lipoprotein, namely, chylomicrons and VLDL. Lipase was named lipoprotein lipase by Korn, who showed that the enzyme hydrolyses chylomicron triglycerides. LPL is probably located close to the capillary wall and that there is a direct relationship between

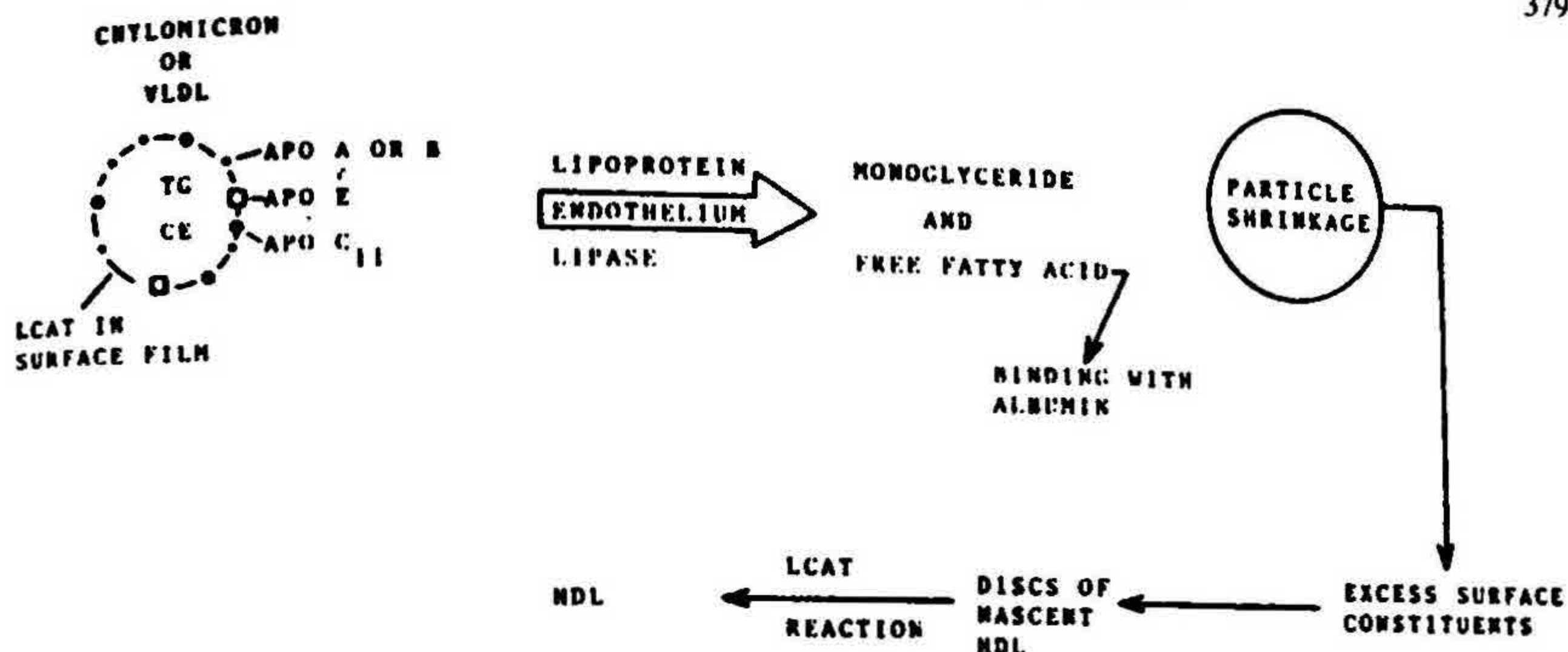


FIG. 4. Schematic diagram showing hydrolysis of TG in chylomicrons and VLDL by endothelial lipoprotein lipase.

the level of tissue LPL activity and the rate of lipoprotein triglyceride uptake<sup>28</sup>. In the past 20 years, LPL has been the subject of extensive research, particularly in connection with the mechanism of hydrolysis of triglyceride-rich lipoproteins, regulation of enzyme activity, relationship between the enzyme in parenchymal cells, etc.

#### a) Mechanism of binding to the endothelium

The rapid release of LPL indicated that its location is close to the vascular lumen, suggesting that heparin interacts with the enzyme and releases it from the capillary endothelium<sup>29</sup>. It was initially thought that heparin might be an integral part of the enzyme, necessary for catalytic activity. However, recent studies with purified preparations of LPL show that it contains less than 2% heparin and is fully active in the absence of heparin.

Heparin sulfate in the endothelial plasma membrane may be important for two additional aspects of LPL function (fig. 4). It may facilitate the last step in the transport of LPL from its site of synthesis to the luminal surface of the endothelium. Furthermore because of electrostatic attraction between sulfated glycosaminoglycans and lipoproteins, it may enhance the interaction between lipoprotein lipase and circulating lipoprotein particles. Figure 4 shows the detailed mechanism of LPL action on hydrolysis of circulating triglycerides and formation of HDL.

#### b) Substrate specificity

Substrate specificity studies have shown a positional specificity for the primary ester bonds of triglycerides and diglycerides. Fatty acid chain length and degree of unsaturation do not seem to affect the activity of milk LPL<sup>30</sup>. *In vitro*, monoglycerides accumulate during the hydrolysis of chylomicron triglyceride present in several tissues and in platelets. Under certain conditions, monoglycerides are hydrolyzed by LPL<sup>31</sup>.

## 2.6. Lipoprotein lipase in disease

### a) LPL in diabetes

Hypertriglyceridemia is a common feature of untreated *Diabetes mellitus* that is probably associated with low activity of adipose tissue LPL<sup>32</sup>. The impaired triglyceride clearance in diabetes can be restored to normal by insulin therapy, which leads to an increase in adipose tissue LPL activity. It was recently shown that, although plasma insulin levels during glucose tolerance tests were comparable to obese controls, diabetic, hypertriglyceridemic subjects did not maintain normal LPL activity in adipose tissue. These observations confirm earlier data<sup>33</sup> and suggest that unresponsiveness to insulin can be overcome by administering more insulin. The nature of the diminished response to insulin in adipocytes of diabetic subjects is unknown at present.

### b) LPL in atherosclerosis

Low concentrations of HDL are associated with an increased risk for development of ischemic heart disease. High HDL levels and high LPL activity are present in normal women, in physically well conditioned subjects and in diabetics receiving insulin treatment. Conversely, both LPL and circulating HDL levels are low in type I and V hyperlipoproteinemia and in diabetes untreated.

The relationship between LPL levels and circulating HDL levels was recently studied in several subjects from kindreds with familial hyperalpha-lipoproteinemia. The latter is an inherited condition, characterized by higher life expectancy. The role for lipoprotein lipase in the change in serum lipoprotein levels that occur shortly following myocardial infarctions has recently been suggested<sup>34</sup>. Among these changes is the increase in serum apoprotein CIII, an inhibitor of LPL. The hyperlipemia that follows myocardial infarction may therefore result from lower LPL levels. Low concentrations of high-density lipoproteins are associated with an increased risk of development of ischemic heart disease. A close relationship between the level of HDL cholesterol and triglyceride metabolism is suggested by the reciprocal changes in HDL cholesterol and VLDL triglyceride levels under different conditions such as weight reduction, carbohydrate-rich diet, exercise and alcohol consumption<sup>35</sup>. A glycoprotein purified from porcine aorta was shown to inhibit post-heparin lipolytic activity<sup>36</sup>. This substance named lipolipin was recently isolated from human atherosclerotic intima. Although normal human intimal tissue was not investigated, it is possible that larger amounts of the glycoprotein inhibitor are present in atherosclerotic intima where they may affect lipolysis *in vivo*.

LPL has been postulated as a rate determining enzyme for the clearance of VLDL triglyceride and chylomicron from plasma. The enzyme is a glycoprotein that hydrolyzes acyl-glycerols in plasma lipoproteins at the capillary endothelium. This is a very important step in the utilization of the lipids by the tissues. Therefore, the activity of lipoprotein lipase at the endothelium is an important determinant for the rate of uptake of lipoprotein lipids by many tissues and the activity responds rapidly to changes in the nutritional and hormonal state. The exact relationship between LPL modulation of serum lipoprotein content and composition and the process of atherogenesis remains to be



elucidated. This could form one of the areas of future research in the biochemistry of lipoproteins.

### Acknowledgement

The study was supported by grants from the Council of Scientific and Industrial Research and the All India Institute of Medical Sciences, New Delhi. Thanks are due to Sandhya Chanda for secretarial assistance.

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