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Discussion

The VLDL receptor plays a key role in the metabolism of postprandial remnant lipoproteins

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ABSTRACT

A new concept to account for the process of postprandial remnant lipoprotein metabolism is proposed based on the characteristics of lipoprotein particles and their receptors. The characteristics of remnant lipoprotein (RLP) were investigated using an immuno-separation method. The majority of the postprandial lipoproteins increased after fat intake was shown to be VLDL remnants, not chylomicron (CM) remnants, based on the significantly high ratio of apoB100/apoB48 in the RLP and the high degree of similarity in the particle size of the apoB48 and apoB100 carrying lipoproteins, which fluctuate in parallel during a 6 h period after fat intake. The VLDL receptor was discovered as a receptor for TG-rich lipoprotein metabolism and is located in peripheral tissues such as skeletal muscle, adipose tissue, etc., but not in the liver. Postprandial VLDL particles are strongly bound and internalized into cells expressing the VLDL receptor. Ligands that bind to VLDL receptor, such as LPL and Lp(a), present in RLP. The presence of various specific ligands in VLDL remnants may enhance the capacity for binding to the VLDL receptor, which play the role primarily for energy delivery to the peripheral tissues, but is also a causal factor in atherogenic diseases when excessively and/or continuously remained in plasma.

1. Introduction

Elevated postprandial remnant lipoproteins (RLP) have been investigated as a research target in atherosclerosis and cardiovascular disease. However, we recently reported that the formation and role of postprandial remnants are linked with certain metabolic pathways that are essential for energy (i.e. free fatty acids (FFAs)) delivery to the peripheral tissues [1–3]. Fat intake, not carbohydrate, is the major initiation triggering event for the formation of RLP, which originate from chylomicrons (CM) in the intestine and very low density lipoproteins (VLDL) in the liver. Two different kind of remnants in the blood circulation have been known since the 1960s [4,5]. These are CM remnants of exogenous origin and VLDL remnants of endogenous origin, which are believed to be under the control of different metabolic pathways. Nakajima et al. [6,7] isolated RLP from plasma that contain both apoB48 (CM) and apoB100 (VLDL) particles using a monoclonal antibody (Mab) to apoB (JI-H) and separated out VLDL remnants enriched in apoE and apo C3 [8,9] that have a larger particle size and are cholesteryl ester rich (Figs. 1, 2). These particles are expressed in normolipidemic subjects as well as patients with exogenous and endogenous hypertriglyceridemia as well as familial dysbetalipoproteinemia (Type III) (Table 1). Both of these remnant types are formed and respectively metabolized by lipoprotein lipase (LPL), modulated by the cholesterol ester transfer protein (CETP) reaction with HDL, hepatic lipase (HL), and the exchange of soluble apolipoproteins such as C-I, C-II, C-III and E. They are significantly increased after fat intake [4,5]. These remnants are found in the plasma as the major triglycerides (TG) in the CM and VLDL fractions after fat intake, exhibiting a similar particle size as apoB48 and apoB100 carrying RLP particles [10], but are different from the fasting or nascent CM and VLDL [11]. CM particles are formed in the intestine from hydrophobic long-chain fatty acids and secreted into the circulation through the lymph duct. CM remnants are then formed at the endothelium by LPL hydrolysis, secreted into the circulation and cleared within a very short period of time (5–12 min) [12,13]. If LPL activity is deficient because of an LPL gene mutation or the presence of GPIHBP1 autoantibodies, CM is unable to CM remnants and the result is chylomicronemia [14] (Fig. 3). CM remnants are mostly incorporated into the liver after fat intake. However, VLDL remnants are secreted into the circulation after VLDL particles are formed in the liver. VLDL remnants are formed at the

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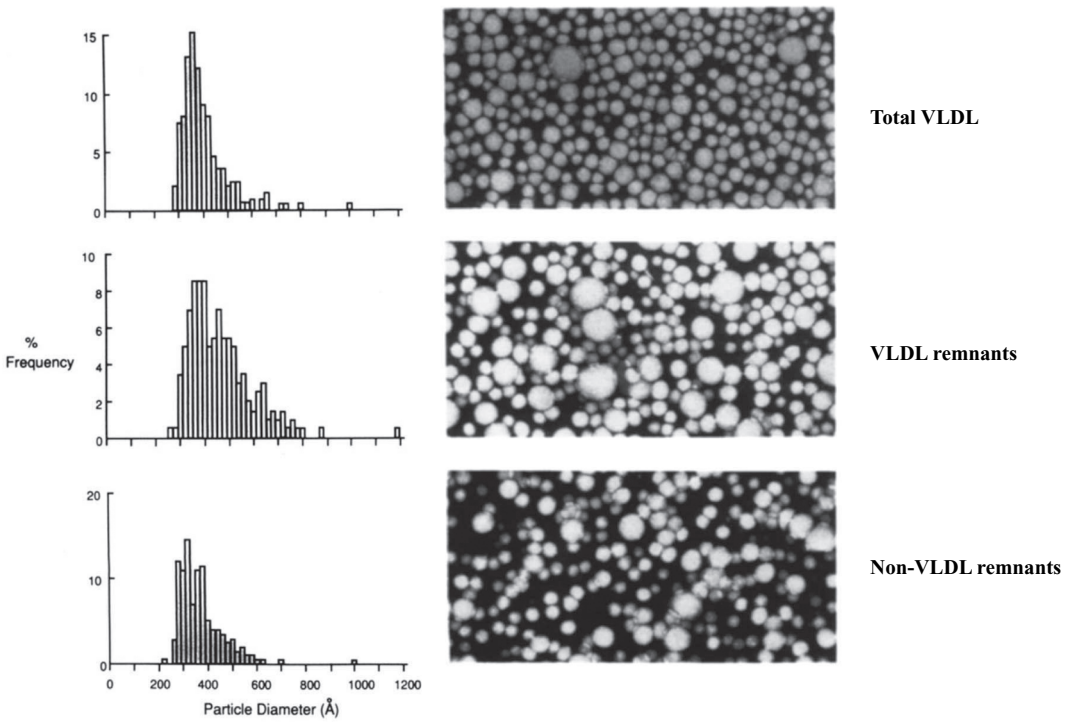


Fig. 1. Distribution patterns of the VLDL particle diameter and its two Mab (JI-H) fractions from a patient with Type III. Top: total VLDL, Middle: RLP fraction, bottom: bound fraction. Left: particle diameter, Right: corresponding electron photomicrograph. The remnant fraction has a larger VLDL particle size than that of the non-remnant fraction. (Ref. 8, Campos et al. J Lipid Res 33 (1992) 369–380).

endothelium by LPL hydrolysis, similar to the case of CM remnants, and increase in the plasma 2–6 h after fat intake [1–3]. VLDL remnants are delivered to peripheral tissues and used as an energy source (i.e. TG), much like blood glucose.

However, it has long been believed that CM remnants are secreted from the intestine into the circulation after fat intake and play a key role as atherogenic lipoproteins since Zilversmit first proposed it [15]. This is because apoB48, which is a unique apolipoprotein specific to CM, increases and decrease in parallel with the postprandial TG level [10,11]. However, we speculated that the majority of CM remnants after fat intake are directly incorporated into the liver and there reformed into VLDL constituents, and then secreted into the circulation as VLDL remnants carrying apoB48 [2]. The notion of CM remnants increasing as major lipoproteins in plasma after fat intake has confusion in terms of the overall concept of postprandial remnant lipoproteins. Therefore, we have proposed that the majority of postprandial remnants are not CM remnants but rather, VLDL remnants, which are reconstructed in the liver from CM remnants after fat intake [2]. Among the specific receptors and their ligands which are associated with the metabolism of postprandial RLP, we have described the 4 different receptors reported to interact with RLP in this manuscript. There are two types of remnant receptors; one is the receptor for CM remnants which plays the major role in incorporating CM remnants into the liver. The VLDL receptor plays the major role in incorporating VLDL remnants in the peripheral tissues. We have hypothesized that the most important receptor for postprandial remnant metabolism is the VLDL receptor, which plays an essential role for the incorporation of energy (FFA) in the peripheral tissues. The atherosclerotic diseases are induced when postprandial remnants are maintained at an elevated level in the plasma over time as the result of excessive fat intake [1].

2. The receptors known to interact with remnant lipoproteins

Four different receptors are reported to interact with remnant lipoproteins. However, it has not been cleared which of these is the major receptor for the metabolism of postprandial remnant lipoproteins. As the characteristics and the roles of these receptors have been reported previously, we have tried to compare the function of those receptors on the postprandial remnant metabolism.

2.1. The LDL receptor

The LDL receptor is one of the representative receptors that interact with remnant lipoproteins through apolipoprotein E (apoE), and is mainly expressed in the liver [16]. The members of the LDL receptor family are strongly associated with apoE-rich lipoproteins, specifically remnant lipoproteins, and mediates their interactions. ApoE exists in three common isoforms that have distinct functional and biological properties. Two apoE isoforms, apoE3 and apoE4, are recognized by the LDL receptor, whereas apoE2 binds poorly to the LDL receptor and is associated with type III hyperlipidemia. In addition, the apoE4 isoform is associated with the common late-onset familial and sporadic forms of Alzheimer's disease. Ruiz et al. [17] characterized the binding of apoE to the VLDL receptor and LDL receptor related protein (LRP). Their results indicate that like the LDL receptor, LRP prefers lipid-bound forms of apoE, but in contrast to the LDL receptor, both the LRP and VLDL receptor recognize all of the apoE isoforms. Interestingly, the VLDL receptor does not require the association of apoE with lipid for optimal recognition and avidly binds lipid-free apoE. It is likely that this receptor-dependent specificity of the various apoE isoforms and for lipid-free versus lipid-bound forms of apoE is physiologically significant and connected to the distinct functions of these receptors. The structure of apolipoprotein E receptor 2 (ApoER2; LRP8) is similar to that of the LDL receptor and VLDL receptor, as shown in Fig. 3, and is a receptor known for mediating signaling initiated by reelin in neurons [18], but it is currently unknown whether it is associated with postprandial remnant metabolism.

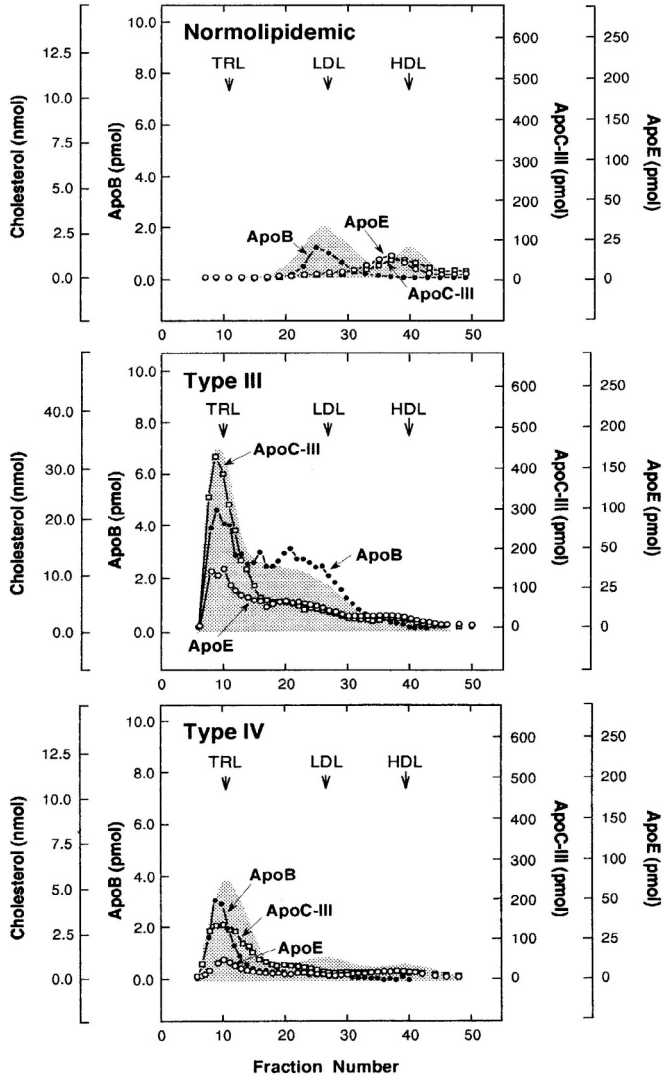


Fig. 2. Separation of lipoproteins in the RLP fraction according to size by automated gel filtration chromatography on an FPLC system. Results are shown for RLP from the plasma of a normolipidemic subject (top panel), a type III patient (middle panel), and a type IV patient (bottom panel). The elution profile of cholesterol is indicated by the shaded areas, and the elution of lipoproteins corresponding to the VLDL, LDL or HDL size is indicated by an arrow in each panel. The amounts of apoB and apoE in each elution fraction are indicated by the closed and open circles, respectively, while apoC-III is indicated by the open square. (Ref. 9, Marcoux et al. J Lipid Res 40 (1999) 636–47).

2.2. LDL receptor related protein (LRP)

The LRP is a cell surface receptor that binds and internalizes a number of macromolecules, including apo *E*-enriched remnant lipoproteins and protease-antiprotease complexes such as activatedα2-macroglobulin, and is mainly expressed in the liver. Its function has been studied primarily in cultured fibroblasts and the liver. Descamps et al. [19] reported evidence that LRP is present on the surface of primary adipocytes isolated from rat epididymal fat pads. The activity of the receptor increases 2–3-fold within minutes after the adipocytes are exposed to physiological concentrations of insulin, as indicated by an increase in the uptake of ^{125}I-labeled activatedα2 macroglobulin. There is a corresponding increase in the uptake of ^{3}H-cholesteryl esters from radiolabeled apoE-enriched VLDL. The latter uptake was reportedly inhibited by an antibody against LRP and by a fusion protein containing the 39-kDa receptor-associated protein (RAP), a known inhibitor of LRP function [20]. Rats treated in vivo with RAP that had been fed ad libitum accumulated approximately 24-fold more chylomicron cholesteryl esters in their epididymal fat pads than did fasted control animals. These results indicate that LRP plays the important role of CM remnants incorporation in the liver. Descamps et al. [19] suggested that synergistic insulin stimulation of LRP together with lipoprotein lipase increases the endocytic uptake of cholesterylesters and triglycerides from remnant lipoproteins in postprandial adipocytes.

2.3. Lectin-like oxidized LDL receptor-1(LOX-1) receptor

Sawamura et al. [21] discovered and characterized the lectin-like oxidized LDL receptor-1 (LOX-1) as a vascular endothelial receptor for Ox-LDL. Endothelial dysfunction or activation of this receptor invoked by oxidatively modified LDL has been implicated in the pathogenesis of atherosclerosis by enhanced intimal thickening and lipid deposition in the arteries. Ox-LDL and its lipid constituents, which are mainly composed of oxidized phospholipid products such as lysophosphatidylcholine, impair the endothelial production of nitric oxide. They also induce the endothelial expression of leukocyte adhesion molecules and smooth muscle growth factors, which can contribute to atherogenesis via the LOX-1 receptor. Vascular endothelial cells in culture and in vivo internalize and degrade Ox-LDL through a putative receptor-mediated pathway that does not involve the macrophage scavenger receptor. The above characteristics of Ox-LDL display a strong similarity with RLP [22]. The treatment of HUVECs with RLP increased LOX-1 receptor expression dose-dependently and this effect was completely inhibited by LOX-1-antisense, but not LOX-1-sense. A monoclonal antibody to the LOX-1 receptor reported by Shin et al. [23] and an antisense LOX-1 oligodeoxynucleotide reported by Park et al. [24] significantly reduced the RLP-mediated production of superoxide (NADPH oxidase-dependent activity), TNF-alpha, interleukin-beta, NF-κB activation, and DNA fragmentation (i.e. cell death: apoptosis). Furthermore, Shin et al. [23] have emphasized the importance of RLP in increasing the expression of the LOX-1 receptor in the course of NADPH oxidase dependent superoxide production. The expression of the adhesion molecules such as ICAM-1, VCAM-1 and MCP-1 that are stimulated by RLP is dependent on the activation of the LOX-1 receptor. These findings suggest that the LOX-1 receptor plays a role as a receptor of RLP as well as Ox-LDL in endothelial cells.

Therefore, the LOX-1 receptor enhances the binding and internalization of RLP in a manner similar Ox-LDL, because RLP carries highly oxidative apo(a) which is a ligand to the VLDL receptor [1,28]. Therefore, RLP is able to interact with the LOX-1 receptor as well as VLDL receptor because of the presence of the highly oxidative apo(a) in RLP [1,22].

2.4. VLDL receptor

We provide greater details on the VLDL receptor than the other receptors, because it is known to be closely associated with the binding and internalization of postprandial RLP in peripheral tissues, but not in the liver.

The VLDL receptor was discovered in 1992 by Takahashi et al. [25,26]. It was shown to be distinct from the LDL receptor and to play a role in TG-rich lipoprotein metabolism (Table 2). The VLDL receptor binds apoE-containing lipoproteins, VLDL, β-VLDL and IDL with high affinity, but not LDL. As the result of extensive studies of the VLDL receptor over the last several decades by many researchers, the VLDL receptor has been shown to interact with many ligands contained in RLP, although all of the RLP ligands have not been characterized yet (Table 2). In addition to apoE, the VLDL receptor binds LPL [27], Lp(a) [28], receptor-associated protein (RAP) [19], proprotein convertase subtilisin/kexin type 9 (PCSK9) [29–31], reelin [30,32], thrombospondin-1 [33–35], urokinase plasminogen activator (uPA)/plasminogen activator inhibitor-1 complex [36–39], serine protease-serpin complex [40], and tissue factor pathway inhibitor (TFPI) [39].

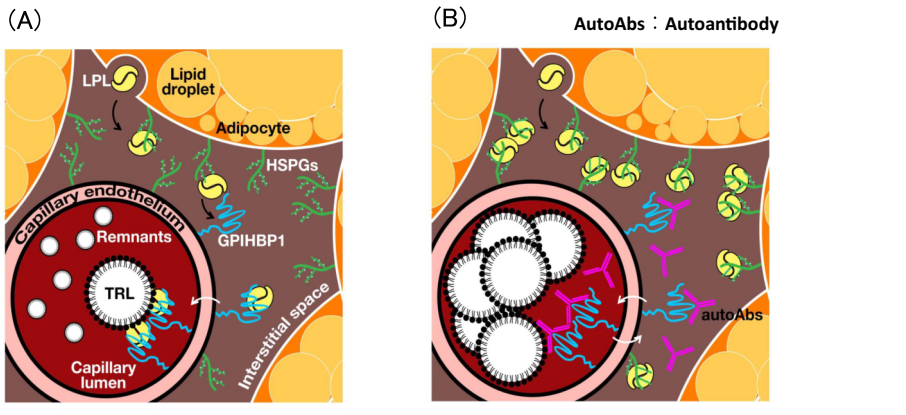
Table 1
Composition and size of VLDL unbound(RLP) and bound (non- VLDL remnants) to Mab JI-H.

	Normolipidemia (n = 3)		Endogeneous Hypertriglyceridemia (n = 5)		Familial Dysbetalipoproteinemia (n = 3)		Lipoprotein Lipase Deficiency (n = 1)	
	Unbound	Bound	Unbound	Bound	Unbound	Bound	Unbound	Bound
				weight %				
Choresteryl ester (CE)	5.5 ± 0.95	6.4 ± 1.8	11.0 ± 2.5	14.2 ± 3.2	23.3 ± 6.4	22.2 ± 5.3	10.5	11.5
Triglyceride	60.8 ± 2.8	54.4 ± 3.2	54.3 ± 2.5	46.1 ± 3.7	40.9 ± 7.6	38.1 ± 5.4	66	48.8
Choresterol	6.1 ± 1.5	7.0 ± 1.1	6.9 ± 1.8	8.0 ± 0.95	8.2 ± 1.7	8.3 ± 1.6	5.2	6.3
Phospholipids	17.2 ± 0.7	17.9 ± 0.5	19.6 ± 2.2	20.4 ± 1.8	20.5 ± 3.6	21.1 ± 3.2	14.1	22.1
Protein	10.4 ± 1.1	14.3 ± 1.4[a]	8.2 ± 1.3	11.4 ± 1.2[a]	7.1 ± 1.4	10.3 ± 1.0[b]	4.2	11.3
Median particle diameter (Å)	495[c]	390	417 ± 57[d]	342 ± 28	432[e]	377	576	403
Mass ratios								
CE:apoB	2.6 ± 0.13[f]	1.7 ± 0.7[f]	3.2 ± 1.3	2.3 ± 0.36	7.3 ± 2.9	5.1 ± 2.3[b]	6.0	2.0
ApoE:apoB	0.42 ± 0.15	0.14 ± 0.11[b]	0.24 ± 0.11	0.13 ± 0.045[b]	0.34 ± 0.13	0.13 ± 0.052[b]	0.30	0.072
ApoE:apoC	0.13 ± 0.01	0.059 ± 0.01	0.12 ± 0.14	0.12 ± 0.14	0.44 ± 0.29	0.13 ± 0.10[b]	0.28	0.080

Values given as mean ± SD.
[a] $P < 0.02$.
[b] $P < 0.05$.
[c] $n = 1$.
[d] $n = 3$.
[e] $n = 2$.
[f] ApoB measured by immunonephelometry.

Therefore, the interaction between the VLDL receptor and VLDL remnants has become a subject of major interest in the effort to establish a better understanding of remnant lipoprotein metabolism.

A cDNA that expresses the VLDL receptor was isolated from a rabbit heart cDNA library and characterized by Takahashi et al. [25]. The VLDL receptor structure appears to be very similar to the LDL receptor and apoE R2 (Fig. 4), but its function is very different. The deduced amino acid sequence of the cDNA revealed that it encodes a protein with striking homology to the LDL receptor. Like the LDL receptor, the mature protein consists of the following five domains spanning a total of 846 amino acids: 328 N-terminal amino acids, including an 8-fold repeat of 40 amino acids homologous to the ligand binding repeat of the LDL receptor; 396 amino acid residues homologous to the epidermal growth factor precursor, including three cysteine-rich repeats; a region immediately outside of the plasma membrane rich in serines and threonines; 22 amino acids traversing the plasma membrane; and 54 amino acids containing the NPVY sequence that is required for the clustering of the LDL receptor in coated pits and that projects into the cytoplasm. LDL-receptor-deficient Chinese hamster ovary cells transfected with the VLDL receptor cDNA were shown to bind and internalize VLDL,β-migrating VLDL, and intermediate density lipoprotein (IDL), but do not bind LDL with a high affinity. The 3.6- and 9.5-kilobase mRNAs for the VLDL receptor are highly abundant in heart, muscle and adipose tissue. Barely detectable amounts of the mRNAs are present in the liver. Based on the structural features, ligand specificity and tissue expression of the mRNAs, Takahashi et al. [25,26] have suggested that this VLDL receptor may mediate the uptake of apoE-containing lipoproteins enriched with triglyceride in non-hepatic tissues that are active in fatty acid metabolism. The VLDL receptor is involved in the tissue delivery of VLDL-TG derived FFAs by facilitating the expression of LPL. However, VLDL receptor deficient mice do not exhibit altered plasma lipoprotein levels on standard lab chow, despite reduced LPL expression. Because LPL activity is crucial in postprandial lipid metabolism, Goudriaan et al. [41] investigated whether the VLDL receptor plays a major role in chylomicron clearance. The plasma TG levels of VLDL receptor deficient mice were increased 2.5-fold by high fat diet compared with their normal VLDL receptor littermates. Strikingly, an intra-gastric fat load led to a 9-fold increased postprandial TG response in the VLDL receptor deficient mice compared with normal mice. Accordingly, the plasma clearance of [^{3}H]TG-labeled protein-free



Capillary Lumen of Normal Control **Capillary Lumen in Patient with GPIHBP1 Autoantibodies**

Fig. 3. Normal lipolysis and defective triglyceride processing in GPIHBP1-autoantibody syndrome. Panel A shows the normal intravascular processing of triglycerides in a healthy person, and Panel B shows defective triglyceride processing in a patient with the GPIHBP1-autoantibody syndrome. Normally, the lipoprotein lipase that is secreted by parenchymal cells (e.g., adipocytes and myocytes) is captured by GPIHBP1 on the basolateral surface of endothelial cells. GPIHBP1 then transports lipoprotein lipase across endothelial cells to the capillary lumen, where the lipoprotein lipase hydrolyzes the triglycerides in triglyceride-rich lipoproteins (e.g., very-low-density lipoproteins and chylomicrons). GPIHBP1 autoantibodies block the binding of lipoprotein lipase to GPIHBP1 and therefore block the transport of lipoprotein lipase to the capillary lumen, resulting in an accumulation of triglyceride-rich lipoproteins in the plasma (hypertriglyceridemia). HSPG denotes heparan sulfate proteoglycan, and TRL triglyceride-rich lipoprotein.

Table 2
Different characteristics between VLDL receptor and LDL receptor.

	VLDL receptor	LDL receptor
Gene location	9p24	19p13.2
Phenotype of human mutant	Cerebellar hypoplasia with cerebral gyral simplification	Familial hypercholesterolemia (FH)
Ligands	ApoE, LPL, Lp(a), RAP, PCSK9, Reelin, Thrombospondin-1, uPA/plasminogen activator inhibitor-1 complex, Serine protease-serpin complex, Tissue factor pathway inhibitor (TFPI), Fibrin, Hepatitis C virus	ApoE, ApoB, RAP, PCSK9, Hepatitis C virus
Main expression sites	Heart, Muscle, Adipose tissue, Macrophages, Endothelial cells, Brain	Liver, Adrenal gland
Binding capacity of apoE2/2	Equal to apoE3/3	Less than 1%
Sterol regulation	None	Negative feedback
Alternative splicing	+	−

chylomicron-mimicking emulsion particles was delayed in VLDL receptor deficient mice compared with VLDL receptor normal mice, with a 60% decreased uptake of the label into adipose tissue that did not result in any visceral obesity. VLDL receptor deficiency did not affect the plasma half-life or adipose tissue uptake of albumin- complexed [^{13}C] FFA, indicating that the VLDL receptor facilitates postprandial LPL-mediated TG hydrolysis rather than mediating FFA uptake. The authors concluded that the VLDL receptor plays a major role in the metabolism of postprandial lipoproteins by enhancing LPL-mediated TG hydrolysis.

Goudriaan et al. [42] also reported that the VLDL receptor plays a key role in the obesity and insulin resistance that occurred when mice are fed a high-fat refined-sugar (HFS) diet. This indicates that the TG (i.e. the TG in the VLDL remnants) that were increased in plasma by HFS did not result in the storage of TG in adipose tissue in the absence of the VLDL receptor, and thus did not induce the enlargement of adipocytes or insulin resistance [1]. Therefore, the VLDL receptor plays the key role in the metabolism of postprandial remnant lipoproteins.

In humans, VLDL receptor deficiency has been reported in Hutterite families having autosomal recessive cerebellar hypoplasia with cerebral gyral simplification [43,44] (Table 2). Although the lipid levels were not reported in these VLDL receptor-deficient families, it is interesting that 50% of the affected patients were underweight, with a body mass index (BMI) of 18.5. Thus, there is suggestive evidence that VLDL receptor deficiency protects against obesity in both humans and mice, establishing phenotypic parallels between the human and mouse VLDL receptor deficient state.

3. Postprandial remnant lipoprotein metabolism

The ligands of the VLDL receptor found on VLDL remnants enhance the binding and internalize the VLDL remnants in peripheral tissues. Apo E is the most typical ligand for the receptors, while LPL and Lp(a), which are known to be VLDL receptor ligands, are also found in VLDL remnants. Adiponectin, metallothionein and PCSK9 seem to affect the function of the VLDL receptor. Therefore, these factors may either enhance or interfere with the interaction between the VLDL remnants and VLDL receptor.

3.1. The LPL bound to postprandial VLDL remnants is a ligand for the VLDL receptor

ApoE-rich VLDL is the defining characteristic of VLDL remnants and apoE is known to be a ligand for the VLDL receptor as well as the LDL receptor [25–27]. In addition to these apolipoproteins in RLP, we have recently reported the presence of LPL and Lp(a) in isolated RLP. LPL [27] and Lp(a) [28] have already been reported to be ligands of the VLDL receptor, but their presence has not been reported in postprandial RLP.

Sato et al. [45] reported that LPL binds directly to plasma remnant lipoprotein particles (i.e. the RLP-LPL complex), which we have reported as “RLP” since 1993 [6–10,22,46] (Table 3). The RLP-LPL

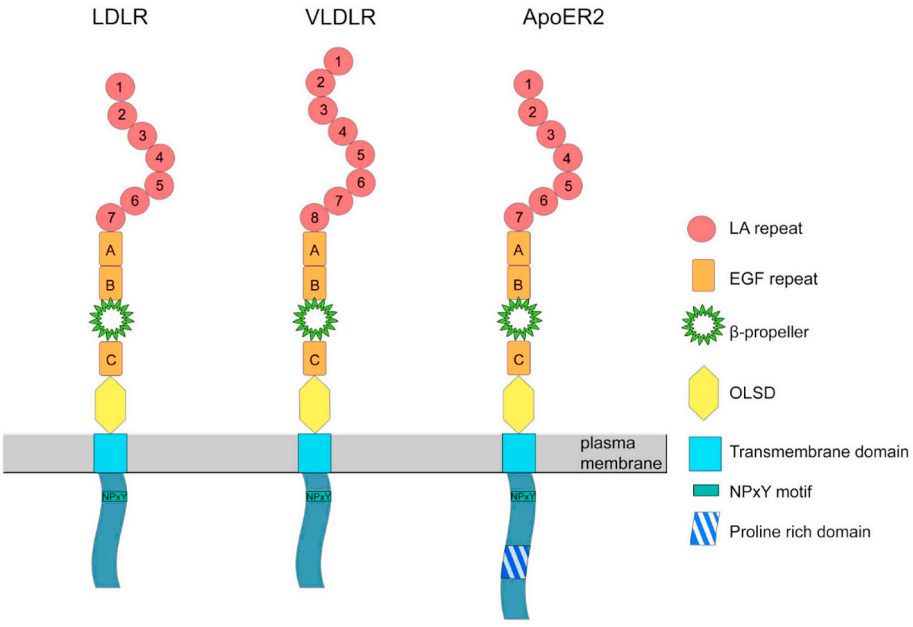


Fig. 4. Structural comparison of the LDL, VLDL, and Apo E receptor. All three receptors react with apoE-rich lipoproteins and have very similar structural composition, but different localizations and functions.

Table 3
LPL concentration in RLP fraction (RLP-LPL) in pre-heparin and post-heparin plasma of 29 healthy volunteers.

	Pre-heparin	Post-heparin	Pre-heparin –Post-heparin	p Value
TC(mg/dL)	174 ± 33	169 ± 32	−5 ± 8	NS
TG(mg/dL)	139 ± 78	103 ± 58	−36 ± 24	P < 0.01
LDL-C(mg/dL)	102 ± 28	100 ± 27	−2 ± 5	NS
HDL-C(mg/dL)	49 ± 13	47 ± 12	−2 ± 3	NS
RLP-C(mg/dL)	7.2 ± 4.6	6.7 ± 4.1	−0.5 ± 1.2	NS
RLP-TG(mg/dL)	44.6 ± 36.9	25.5 ± 24.4	−19.1 ± 18.3	P < 0.01
RLP-TG/RLP-C	6 ± 1.7	3.5 ± 1.4	−58% ± 13%	P < 0.01
Plasma LPL (ng/mL)	81 ± 27	438 ± 95	357 ± 89	P < 0.01
RLP-LPL (ng/mL)	62 ± 26	117 ± 30	64 ± 23	P < 0.01
RLP-LPL/Plasma LPL (%)	77 ± 11	27 ± 5	NC	P < 0.01
RLP–LPL/RLP-C (%)	9.7 ± 7.8	23.2 ± 14.8	NC	P < 0.01

complex exhibits the following characteristics. 1) > 80% of the circulating LPL in the pre-heparin plasma is found in RLP as the RLP-LPL complex. 2) The circulating LPL found in RLP in the pre- and post-heparin plasma was shown to be in the inactive form. 3) When lipolytic activity was inhibited by tetrahydrolipstatin (THL) in the post-heparin plasma, most LPL was found in the VLDL elution range, specifically especially in RLP (Fig. 5). When the ex vivo lipolytic activity was not inhibited by THL, LPL became transitional in the post-heparin plasma and was shown to shift rapidly to the HDL elution range by HPLC analysis. 4) Two different types of LPL are present in the post-heparin plasma; one is the active form, found mostly in the HDL elution range, while the other is the inactive form found in RLP. These results provide new insight into LPL in the circulating plasma. As reported by Takahashi et al. [27], the presence of LPL on RLP enhances the reactivity to the VLDL receptor.

Beisiegel et al. [47] analyzed the binding of human CM to HepG2 cells in the presence and absence of LPL. Both bovine and human LPL were able to increase the specific binding of CM by up to 30-fold. This effect was not dependent on lipolysis and appeared to be due to the lipase protein itself. This did not occur when a structurally unrelated bacterial lipase was used. Usingβ-VLDL, which is known to be a good ligand for LRP, binding studies were performed on LDL receptor-negative human fibroblasts. The binding was increased 40-fold by the addition of LPL. Crosslinking experiments on cells with ^{125}I-labeled apoE liposomes or LPL showed that both proteins were able to bind to the LRP on the cell surface. The binding of apoE to LRP was greatly increased by the addition of LPL. Beiseigel et al. [47] concluded that LPL strongly enhances the binding of apoE-containing lipoproteins to LRP and therefore might play an important role in CM catabolism, not only because of its lipolytic activity, but also its structural properties. Although the VLDL receptor is not expressed as LRP in the liver, these results nevertheless point to the importance of LPL as a ligand to the VLDL receptor.

3.2. Apolipoprotein (a) (Lp(a)) bound to postprandial VLDL remnants is a ligand for the VLDL receptor and increase after a fat load

Argraves et al., [28] reported that the atherogenic lipoprotein Lp(a) is internalized and degraded in a process mediated by the VLDL receptor. The mechanism of Lp(a) atherogenicity has not been elucidated, but likely involves both its ability to influence plasminogen activation as well as its atherogenic potential as a lipoprotein particle after VLDL receptor-mediated uptake. Diffenderfer et al. [48] reported that the apo (a) within Lp(a) in the VLDL density region is in part directly catabolized and converted into a cholesterol-rich particle with a density similar to that of LDL. They speculated that during catabolism of Lp(a), apo(a) dissociates from apoB-100 and may associate with newly-formed VLDL apoB-100 containing particles, thereby extending the plasma residence of apo(a) relative to the apoB-100 within Lp(a). Therefore, they speculate there is a RLP-apo(a) complex in plasma after a fat load.

Bersot et al. [49] reported that fat ingestion in humans induces lipoproteins of a density < 1.006 g/ml that are enriched in Lp(a) and that cause lipid accumulation in macrophages. Formula diets containing lard or lard and egg yolks were fed to six normolipidemic volunteers to investigate subsequent changes in the composition of lipoproteins of d < 1.006 g/ml and their capacity to bind and be taken up by receptors on mouse macrophages. Both formulas induced the formation of d < 1.006 lipoproteins that were ~3.5-fold more active than fasting VLDL in binding to the receptor forβ-VLDL on macrophages. Subfractionation of postprandial d < 1.006 lipoproteins by agarose

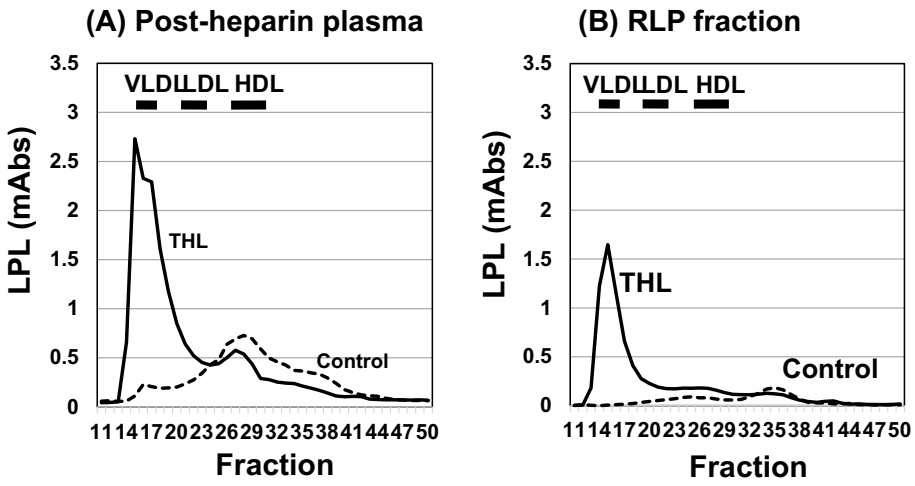


Fig. 5. Effect of an LPL inhibitor (tetrahydrolipstatin: THL) on the gel filtration profiles of LPL and RLP in the post-heparin plasma. (A) A large amount of LPL was found in the VLDL elution range, with additional minor peaks in the LDL and HDL elution range, in the presence of THL. However, in the absence of THL, a small amount of LPL was found in the VLDL elution range, with major peaks in the HDL elution rang. (B) In the RLP, a large amount of LPL was found in the VLDL elution range with minor LDL and HDL elution range peaks in the presence of THL, a pattern which was very similar to the elution profile in the post-heparin plasma. In the absence of THL, however, no LPL was found in the VLDL elution range, with a small amount in the HDL elution range. (Ref. 45, Sato et al. Clin Chim Acta. 461 (2016) 114–125).

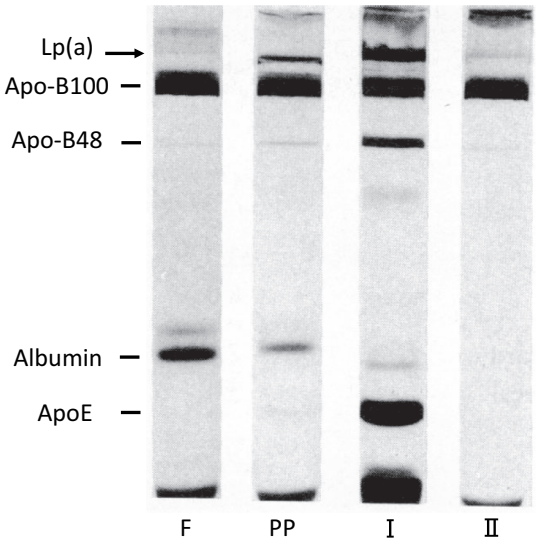


Fig. 6. Polyacrylamide gel electrophoresis of fasting VLDL (F), postprandial d < 1.006 lipoproteins (PP), and fractions I and II (I and II). After delipidation, 30 μg of solubilized protein from each lipoprotein was applied to a 4% acrylamide gel. The buffer contained 0.1% SDS. The arrow indicates a high molecular weight band. Subfractionation of postprandial d < 1.006 lipoproteins by agarose chromatography yielded two subfractions. Fraction I was the VLDL remnants and fraction II was non-remnant VLDL. (Ref. 49, Bersot et al., J. Clin. Invest. 77 (1986) 622–630).

chromatography yielded two subfractions which bound to receptors on macrophages, fraction I (with VLDL remnants contained within it) and fraction II (non-remnant VLDL) (Fig. 6). However, the fraction I lipoproteins induced a 4.6-fold greater increase in macrophage triglyceride content than fraction II. These results clearly show that postprandial remnants contain a significant amount of Lp(a) in the VLDL fraction.

Therefore, we investigated the presence of Lp(a) (i.e. apo(a)) in RLP. Nagawasa et al. [1] reported that apo (a) non-covalently linked to Lp(a) moved to RLP after a fat load without any evident change in the total Lp (a) concentration in plasma, particularly in patients with CVD. The increased apo(a) in RLP was not newly synthesized but rather moved from Lp(a), although RLP was newly synthesized after a fat load. These results reflect the phenomenon Diffenderfer et al. [48] predicted. Among the twenty individuals receiving the oral fat in their study, the cases with CAD displayed significantly increased RLP-apo (a) after the fat load compared with normal controls. Cohn et al. [50] previously reported the plasma lipoprotein distribution of apo (a) in the fed and fasted states. They showed that the percentage of total plasma apo(a) found in the d < 1.006 g/mL fraction increased significantly in response to an oral fat load (from 2% in fasting plasma to 16% postprandially, on average), with no change in the plasma apo(a) concentration. The magnitude of this increase was strongly correlated with the increase in postprandial triglycerides. A similar density redistribution of apo(a) immunoreactivity was observed even more clearly in hypertriglyceridemic subjects rather than normolipidemic subjects. Although it is at present difficult to account for the mechanism of transfer of apo(a) to RLP, apo (a) is heavily glycosylated protein similar to apoE, which is known to transfer among the lipoprotein particles [51].

We have found the concentration of RLP-apo(a) to be in the range of 2–7 mg/dL in the cases we studied, which was approximately 20% of the total plasma Lp(a). The molecular weight (MW) of Lp(a) in serum is mostly reported as being > 500 kDa [52]. However, apo(a) in RLP was shown to have a MW of < 50 kDa by Western blot analysis. This indicates that the apo(a) covalently bound to LDL was not contained in RLP. This means that most of the apo(a) was non-covalently bound to RLP. As the serum and RLP were treated with strong reducing agents such as mercaptoethanol and sodium dodecyl sulfate in preparation for the Western blot analysis [1], the non-covalently linked apo(a) to apoB100 may be cleaved from the KIV2 repeats so as to become a lower MW domain in both serum and RLP. As we found a very similar amount of low MW apo(a) in serum and RLP by Western blot analysis, the RLP carried most of the non-covalently linked apo(a), independently of of Lp (a), in which apo(a) is covalently linked to LDL [53]. The serum RLP-apo(a) concentration in CAD patients increased at 4 h and 6 h after the fat load in correlation with an increase of RLP-C and RLP-TG, but was not significantly increased in healthy controls, similar to the cases Cohn et al. reported [50]. Some of the CAD cases exhibited a > 40% increase in RLP-apo(a), but no such cases were found in healthy controls.

The presence of the RLP-apo (a) complex may explain why RLP are oxidized in the circulation without exhibiting any oxidation in vitro, unlike the case of oxidized LDL. Lp (a), especially the phospholipids of apo (a), is known to be highly oxidized [54]. In particular, this may explain why the postprandial RLP that are increased during the postprandial phase are related to alterations in endothelial function. Shige et al. [55], Maggi et al. [56] and Funada et al. [57] reported studies of alterations of endothelial function in which fasting patients were given an oral fat load and blood samples were collected time-dependently. Endothelial function, determined as the Flow Mediated Dilation (FMD) of the brachial artery, was assessed at the same time points. The postprandial RLP-C exhibited the best correlation with the decrease in FMD. They concluded that RLP contributes significantly to the endothelial dysfunction that occurs in the course of postprandial lipemia. These results support the notion that the oxidized RLP-apo (a) complex that is increased after a fat load may cause endothelial dysfunction as Doi et al. reported [58], possibly through the VLDL receptor on endothelial cells [59]. Karpe et al. [60] reported that lipoprotein remnant particles after a fat load were cleared in adipose tissue and muscle in humans by the VLDL receptor. Since Lp(a) is one of the ligands for the VLDL receptor [28], the RLP-apo(a) receptor pathway and RLP-LPL pathway [45] are potential alternatives for the initiation and progression of insulin resistance and more severe atherosclerotic diseases.

3.3. Postprandial remnants interact more potently with the VLDL receptor than the LDL receptor

> 28 years ago, Takahashi discovered that VLDL and LDL particles in fasting plasma were not recognized by the VLDL receptors overexpressed in cells. He examined postprandial VLDL and LDL particles in a binding study he performed on himself after eating curry rice in the Co-op café at Tohoku University. Postprandial VLDL, but not fasting VLDL and LDL particles, were strongly bound and internalized into the cells which overexpressed the VLDL receptor.

Based on the above observation, Imagawa et al. [61] examined the reactivity of postprandial RLP to the LDL receptor and VLDL receptor in cDNA transfected ldl-A-7 (LDL receptor deficient CHO cell) by using RLP containing CM and VLDL remnants isolated from the postprandial plasma. In the VLDL receptor-transfected cells, as shown in Figs. 7 and 8, RLP was more efficiently bound and internalized through the VLDL receptor than rabbit β-VLDL particles, although no difference in binding capacity was found between RLP and β-VLDL in LDL receptor-transfected cells. Also, RLP binds to the LDL receptor more efficiently than LDL because RLP are apoE-rich [8]. Therefore, RLP competed more efficiently with DiI-β-VLDL than LDL in LDL receptor-transfected cells. These results suggest that RLP is more efficiently bound and internalized into the VLDL receptor and LDL receptor than is LDL. In contrast to RLP, LDL is not recognized by the VLDL receptor, as Takahashi et al. first reported [25].

LDL receptor expression was induced in HepG2 by a low concentration of a statin, while VLDL receptor expression was induced in L6 myoblasts at a higher concentration of the statin. RLP binds to the hepatic LDL receptor more efficiently than LDL, which may explain the mechanism by which statins prevent cardiovascular risk by primarily

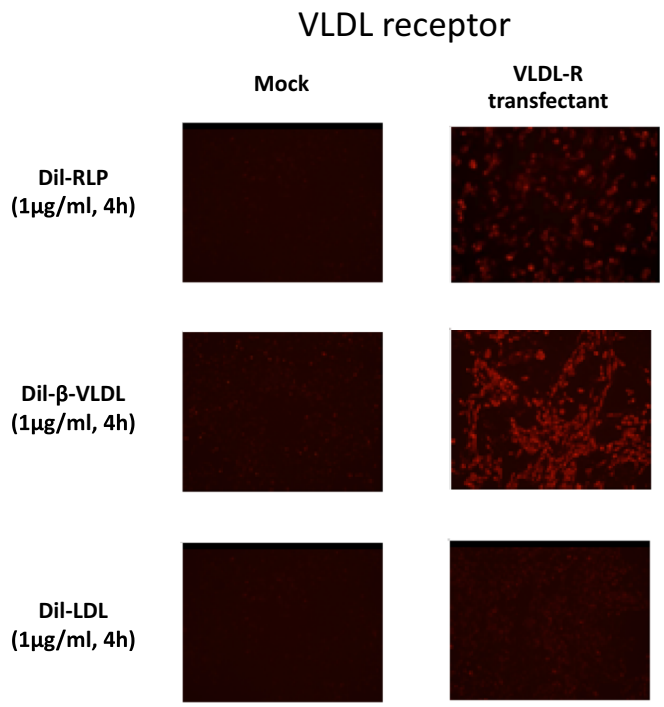


Fig. 7. Binding activity of RLP to the VLDL receptor. LDL receptor-deficient Chinese hamster ovary (ldl-A7) cells were transfected with VLDL receptor cDNA. The pSV2-neo plasmid, which contains the neomycin-resistant gene, were also transfected to ldlA-7 cells and used as a control (Mock). The uptake of lipoproteins in each transfectant was analyzed using DiI-labeled lipoproteins. Cells were incubated for 4 h with 1 μg/ml DiI-labeled RLP, 1 μg/ml DiI-labeledβ-VLDL or 1 μg/ml DiI-labeled LDL and viewed by fluorescence microscopy (magnification ×100). RLP and β-VLDL were bound and incorporated into VLDL receptor-transfected cells at significantly higher levels than LDL. (Ref. 58, Imagawa et al. Clin Chim Acta. 413 (2012) 441–447)

reducing plasma RLP rather than by reducing LDL alone. Additionally, a high-dose of statins also may reduce plasma RLP through the muscular VLDL receptor.

3.4. Knock-out of adiponectin and metallothionein in mice significantly enhances diet-induced obesity

Goudriaan et al. [41,42] reported that VLDL receptor-deficient mice are protected from obesity despite exposure to a high-fat, high-calorie diet (HFD) and have increased plasma triglycerides after HFD feeding. However, mice with adiponectin and metallothionein I/II knock-out, which are significantly localized in adipocytes, are known to exhibit enhanced obesity when fed a HFC diet [62–64]. Therefore, we have hypothesized that these proteins may inhibit the VLDL receptor from incorporating VLDL remnants in visceral adipocytes.

Gua et al. [62] reported that a HFD significantly increased body and organ (heart and liver) weight, heart size (normalized to tibial length), white adipose tissue weight and serum TG concentration, the effects of which were exacerbated by adiponectin deficiency (Fig. 9). Consistent with this, H&E staining revealed that HFD intake evidently increased the cardiomyocyte cross-sectional area, with a more pronounced effect in adiponectin knock-out mice. There was little difference in the myocardial histological appearance between the wild type and adiponectin knock-out mice consuming a low fat diet. Gross morphology exam revealed enlarged hearts in the wild type and adiponectin knock-out mice following high HFD feeding. Furthermore, a HFD triggered dramatic increases in kidney weight and tissue mass (fat mass + lean mass) in the adiponectin knock-out but not wild type mice. In addition, there were no apparent differences in calorie intake or body weight gain between the wild type and adiponectin knock-out mice consuming a low fat diet for 22 weeks. As expected, body weight was significantly increased in the wild type and adiponectin knock-out mice following HFD feeding, the effect of which was exaggerated by adiponectin deficiency as early as two weeks after the HFD intake. From these results, the authors speculated that adiponectin inhibits the function of the VLDL receptor in adipose tissue as well as other peripheral tissues when HFD increased VLDL remnants in the plasma.

Another study by Sato et al. [63] and Lindeque et al. [64] evaluated the protective role of the metallothioneins (MTs; MT 1/2, 3) against obesity and HFD-induced effects such as insulin resistance in both male and female MT-1/2 knockout mice. MT is highly localized in adipose tissues. Oxidative stress accelerates adipocyte differentiation and lipid accumulation, leading to endoplasmic reticulum (ER) stress, which in turn causes insulin resistance. Because MT has a role in the prevention of oxidative and ER stress, Sato et al. [63] examined the effects of MT on the development of obesity induced by 27 weeks of a HFD in female MT-I- and MT-II-null (MT(−/−)) as well as wild-type (MT(+/+)) mice. Body weight, fat mass, and plasma lipids increased at a greater rate in the MT(−/−) mice fed a HFD than MT(−/−) mice fed a control diet (CD) and MT(+/+) mice fed a HFD with the result that the MT(−/−) mice fed a HFD became obese and hypercholesterolemic, and MT was shown to be able to prevent HFD-induced obesity. The observed increases in the levels of plasma leptin and leptin mRNA in the white adipose tissue of MT(−/−) mice fed the HFD suggested a leptin-resistant state. Enhanced expression of a certain mesoderm-specific transcript, which regulates the enlargement of fat cells, was accompanied by enlarged adipocytes in the white adipose tissue of young MT(−/−) mice before obesity developed after 3 and 8 weeks of the HFD. Thus, MT may have a preventive role against HFD-induced obesity by regulating adipocyte enlargement and leptin signaling when consuming a HFD, which may be associated with VLDL receptor function, as shown by Goudriaan et al. [41,42].

3.5. PCSK9 regulates the VLDL receptor as well as LDL receptor

Proprotein convertase subtilisin kexin type 9 (PCSK9) regulates LDL and VLDL receptor expression in several tissue types [28]. Roubtsova et al. [30,31] evaluated whether PCSK9 modulates the handling of TG in the liver and peripheral tissues in mice. In vivo, endogenous PCSK9 regulates VLDL receptor protein levels in adipose tissue. At 6 months of age, Pcsk9−/− mice had accumulated approximately 80% more visceral adipose tissue than wild-type mice. This was associated with adipocyte hypertrophy and increased in vivo fatty acid uptake and ex vivo triglyceride synthesis. This regulation is achieved by circulating PCSK9 that originates entirely in the liver. PCSK9 is thus pivotal in fat metabolism: it maintains high circulating cholesterol levels via hepatic LDLR degradation, but it also limits visceral adipogenesis, most likely via adipose VLDL receptor regulation.

Le May et al. [65] reported that PCSK9-deficient mice clearly exhibited reduced postprandial lipemia after olive oil gavage. Real-time PCR and confocal microscopy were used to show that PCSK9 is expressed throughout the entire small intestine and in human enterocytes. On olive oil gavage, PCSK9-deficient mice showed a dramatically decreased postprandial triglyceridemia pattern compared with their wild-type littermates. Lymph analysis revealed that intestinal TG output is not quantitatively modified by PCSK9 deletion. However, PCSK9−/− mice present with a significant reduction of lymphatic apoB secretion compared to PCSK9+/+ mice. Modulating PCSK9 expression in polarized CaCo-2 cells confirmed the relationship between PCSK9 and apoB secretion; PCSK9−/− mice consistently secrete larger TG-rich lipoprotein than their wild-type littermates. Finally, kinetic studies showed that PCSK9-deficient mice have an increased ability to clear chylomicrons compared to wild-type littermates.These findings indicate that in addition to its effect on LDL-cholesterol, PCSK9 deficiency might

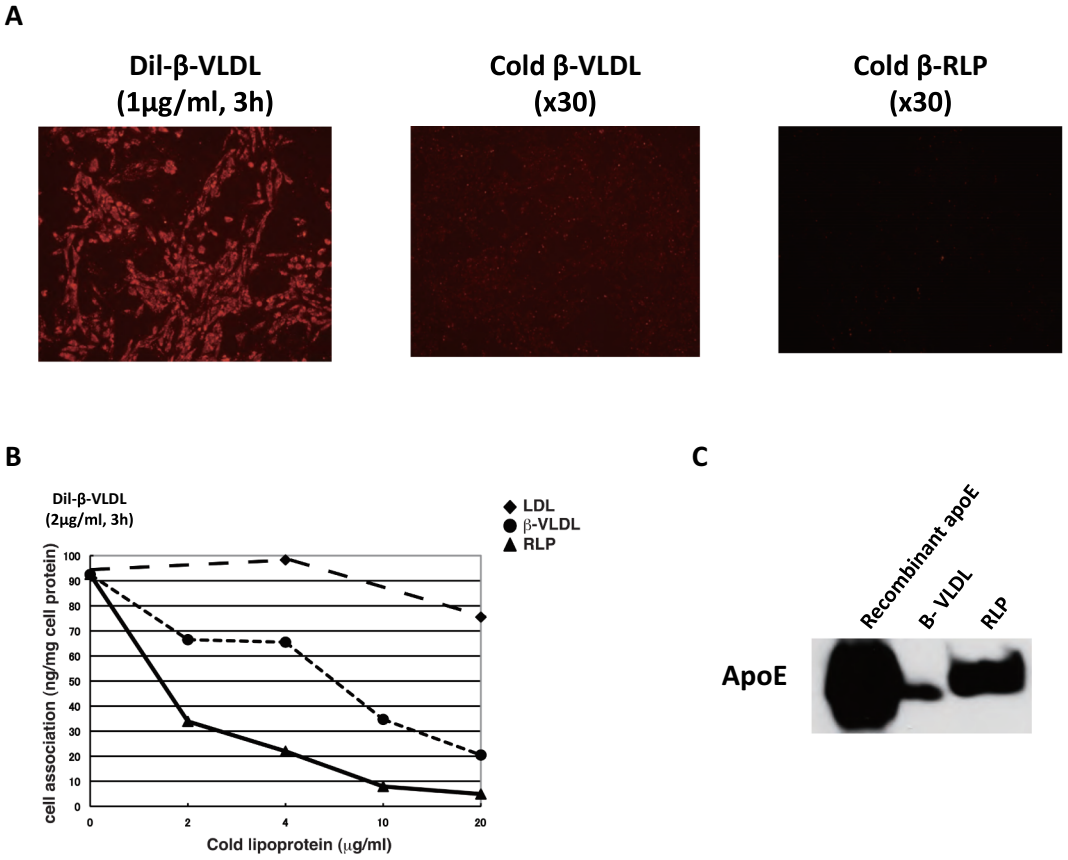


Fig. 8. The binding activity of RLP to the VLDL receptor. (A) Competition studies in VLDL receptor transfectants were performed. Cells were incubated with DiI-labeled β-VLDL in medium containing coldβ-VLDL (30-fold) or cold RLP (30-fold) for 3 h and viewed by fluorescence microscopy (magnification ×100). (B) Cell associations (binding and internalization) of 125I-labeled β-VLDL were measured. VLDL receptor transfectants were incubated with 2 μg/ml 125I-β-VLDL for 3 h in the medium containing cold LDL, β-VLDL and RLP. (C) The amount of apolipoprotein (apo) E in β-VLDL and RLP was checked by Western blot analysis using an antibody against apoE. Recombinant apoE3/3 was used as a positive control.
(Ref. 61, Imagawa et al. Clin Chim Acta. 413 (2012) 441–447)

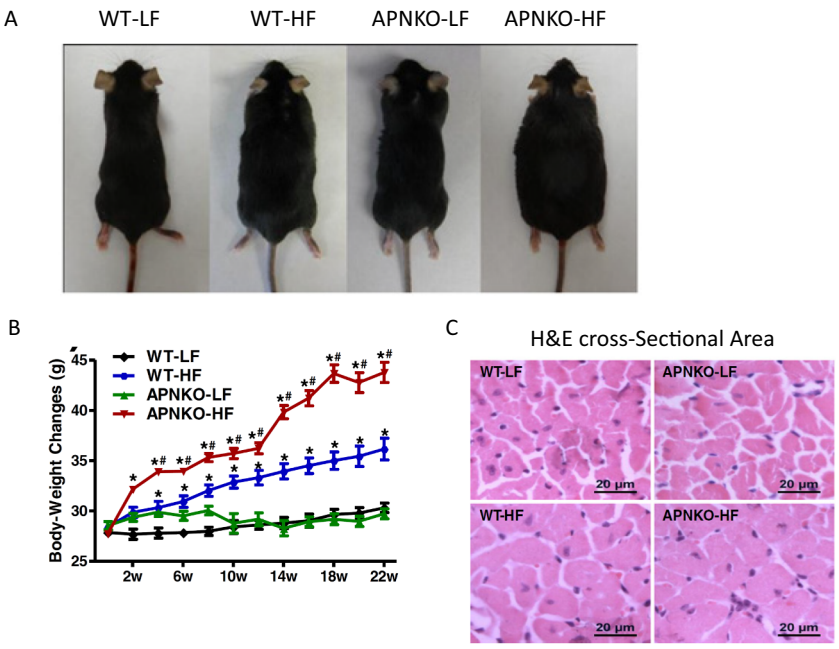


Fig. 9. Effect of adiponectin knockout (APNKO) on high fat diet intake-induced obesity and cardiac hypertrophy. A: Representative photographs of wild type (WT) and APNKO mice fed a low (LF) or high fat (HF) diet; B: Body weight changes of mice fed the LF or HF diet. Mean ± SEM, $n = 9$ mice per group, *p < 0.05 vs. WT-LF group, #p b 0.05 vs. WT-HF group; C: H&E staining micrographs of transverse sections of left ventricular myocardium (×400) from WT and APNKO mice fed the LF or HF diet.
(Ref. 62, Guoa et al., Biochim Biophys Acta. 1832 (2013) 1136–1148).

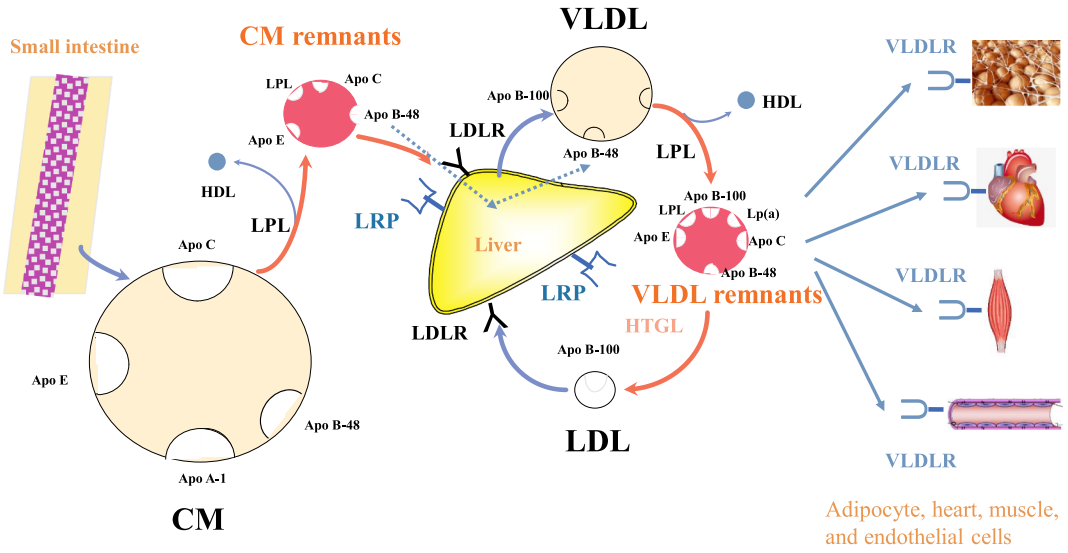


Fig. 10. Metabolic pathway of postprandial lipoproteins after fat intake. The intestine secretes CM, the triglycerides of which are lipolyzed by LPL. The LPL reaction constitutes the initial process in the formation of CM remnants. CM carry LPL as a ligand for the CM remnant receptor in the liver. CM remnants bind and are internalized in the liver and reformed into VLDL. The VLDL secretion process is partly regulated by the rate of FFA from CM remnant influx into the liver. VLDL triglycerides are lipolyzed by endothelial-bound LPL and VLDL remnant particles are formed. The final VLDL remnant composition carries apoB100, apoB48, LPL and Lp(a) and other ligands, and is modulated by the cholesterol ester transfer protein (CETP) reaction with HDL and hepatic lipase (HTGL) as well as the exchange of soluble apolipoproteins such as C-I, C-II, C-III and E. The great majority of the remnants are removed from the plasma by VLDL receptor-mediated processes. The principal receptors for CM remnants are the LDL receptor and LRP in the liver, whereas the VLDL remnants are more likely to bind and be internalized by the VLDL receptor in the peripheral tissues such as the heart, adipocytes, muscle, brain and endothelium.

protect against cardiovascular disease by reducing postprandial triglyceridemia.

Baragetti et al. [66] reported that subjects from the PLIC cohort were genotyped for the loss-of-function PCSK9 R46L variant and characterized for clinical and biochemical parameters, total and android fat mass, hepatic steatosis and epicardial fat thickness. The carriers of the R46L variant had lower LDL-C levels, a higher body mass index and increased percentage of total and android fat masses compared with the non-carriers. The R46L variant was associated with a two-fold increase in the prevalence of hepatic steatosis and a greater epicardial fat thickness.

These findings were replicated in PCSK9 KO mice [64], which displayed increased visceral adipose tissue (but not subcutaneous adipose tissue) compared with wild type mice when fed a normal chow or high-fat diet for 20 weeks. These data suggest that genetically determined PCSK9 deficiency is associated with ectopic fat accumulation, especially in association with the VLDL receptor.

4. The concept of remnant lipoprotein metabolism

Our research has been focused on the postprandial RLP which, similar to blood sugar, fluctuates significantly between the fasting state and after fat intake as a major component of plasma triglycerides [67]. RLP levels are strongly associated with the habits of daily life, such as a kind of food taken and frequency and strength of exercise. We previously reported that RLP may be the “bridge” between the combination of life style factors such as “fat-rich meals and a lack of exercise” and the metabolic disorders of “obesity and insulin resistance” [1]. Although we initially focused on RLP as a causal or risk factor of atherosclerosis, we now recognize that the formation of RLP after fat intake is linked with the essential metabolic pathways for energy delivery to the peripheral tissues. This means that VLDL remnants serve as the major mediator of FFA delivery to the heart, skeletal muscles, adipose tissue, and endothelial cells (Fig. 10) where the VLDL receptor is localized [68]. VLDL remnants and blood sugar are the major sources of TG in adipose tissue for energy preservation as a means to protect against starvation [1]. The mechanism of the storage of TG by the blood sugar associated with obesity and insulin resistance has been well studied [69], but the mechanism by which lipids and lipoproteins from the blood circulation lead to TG storage in adipose tissue is not well established. Therefore, we hypothesized that most of the CM remnants with apoB48 are incorporated into the liver from the circulation very rapidly after fat intake, along with lipids and other apolipoproteins via the LDL receptor, LRP [2], or an unknown pathway, but not via the VLDL receptor. This is because the VLDL receptor, unlike the LDL receptor and LRP, is not expressed in the liver [16,19]. ApoB48 may be reconstituted in VLDL as VLDL-apoB48 by a physiological pathway similar to that of VLDL-apoB100 formation, and then secreted into the circulation as VLDL-apoB48 particles and their remnants [2]. As a result, most of the postprandial remnants that are increased after fat intake are VLDL remnants and interact with the VLDL receptor in peripheral tissues, but are virtually absent in the liver. Therefore, the VLDL receptor plays the major role in the delivery of VLDL remnants to peripheral tissues for the purpose of energy preservation. The LRP and LDL receptors mainly exert their functions when CM remnants bind and internalize into the liver, but may not active in peripheral tissues.

Because of the influential Zilversmit postprandial remnant hypothesis, CM remnants have continued to be believed to be the major remnants in postprandial plasma. We have shown that VLDL remnants are the major postprandial remnants and the VLDL receptor plays the major role in postprandial lipoprotein metabolism. This is because there is a significantly higher ratio of apoB100/apoB48 in RLP in the postprandial plasma [11,70]. Furthermore, the particle size of the apoB48-carrying and apoB100-carrying lipoproteins in RLP was shown to be quite similar and to fluctuate in parallel during a 6 h period after fat intake [10]. From these results, we have concluded that most of the CM remnants are converted to VLDL in the liver and secreted into circulation as VLDL remnants, carrying both apoB48 and apoB-100 in the postprandial lipoprotein particles.

VLDL receptor has been shown to play an important role in TG-rich lipoprotein metabolism and to be distinct from the LDL receptor, with the latter being mainly expressed in the liver. Postprandial VLDL but not fasting VLDL particles are strongly bound and internalized into cells overexpressing the VLDL receptor. Many ligands have been discovered

that bind to the VLDL receptor. We have shown that there are new ligands in RLP, such as LPL and Lp(a) which bind to the VLDL receptor besides apoE. The characteristics of the VLDL receptor reflect the adaptation to specific ligands and the binding of VLDL remnants. These results may account for the fact that VLDL remnants serve as the major mediator of FFA supply to the heart, skeletal muscles, adipose tissue and endothelial cells, where the VLDL receptor is expressed and hence VLDL remnants are incorporated.

5. Conclusion; should the name of the VLDL receptor be changed to the more accurate “remnant receptor”?

When Takahashi et al. first discovered the VLDL receptor in 1992, the differences between VLDL and VLDL remnants were not yet well established. In fact, the composition of VLDL remnants is critically different from the total or fasting VLDL particles. VLDL remnants occupy approximately 1/3 of the total VLDL, which means there is a larger amount of non-remnants in the VLDL fraction. Therefore, the “VLDL receptor” designates a receptor which critically interacts with the non- remnant VLDL as well as VLDL remnants. The biological and biochemical properties of VLDL remnants are very similar to those of Ox-LDL, but non-remnant VLDL does not exhibit such characteristics. Many important new findings on VLDL remnants have been reported over the last decades and the difference between VLDL (either nascent or fasting) and VLDL remnants has become firmly established. Takahashi et al. detailed the characteristics of the activity of the VLDL receptor, which potently interacts with postprandial VLDL remnants but does not interact with fasting VLDL. As shown in Table 1, there may be many potential ligands in RLP not yet clarified which interact with the VLDL receptor. Thus, in conclusion, we would like to propose the “VLDL receptor” name change to the more specifically accurate name of the “VLDL remnant receptor” or, more simply, the “remnant receptor” based on the function of this recptor.

Footnote

We have cited many reports in the literature from our own lab as well as those other researchers in order to establish the new concept of remnants metabolism. We placed our own research results in parentheses in the reference section to differentiate from other researchers' contributions in this manuscript.

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