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Discussion

Hypothesis II: The majority of VLDL-apoB48 remnants in postprandial plasma are derived from the liver, not from the intestine

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ABSTRACT

We have long thought that remnant lipoproteins (RLP) in the postprandial plasma contain CM remnants (exogenous remnants; RLP-apoB48) and VLDL remnants (endogenous remnants; RLP-apoB100) of different origin, i.e. produced in the intestine and liver, respectively. However, the majority of CM remnants incorporated into liver from the circulation are degraded in liver and may be reused for the remodeling of VLDL. Namely, the most of the apoB48 in CM remnants are smoothly incorporated into the liver after fat intake along with lipids and other apolipoproteins via the LDL receptor and LDL-receptor-related protein (LRP). Subsequently, apoB48 may be reconstituted in VLDL as VLDL apoB48 through an essential physiological pathway similar or the same to that of VLDL apoB100 formation in the liver and secreted into the circulation as VLDL apoB48 to form their remnants. Because those particles are newly reconstituted in liver as a portion of VLDL, we propose that both RLP-apoB100 and RLP-apoB48 are endogenous VLDL remnants produced in liver after fat intake. Also we predict the presence of a new pathway for the formation of VLDL apoB48 along with VLDL apoB100 in liver in humans similar in mice and rats.

1. Introduction

Plasma apoB48 is a component of intestinal chylomicrons (CM), which are metabolized to CM remnants by lipoprotein lipase (LPL), and is mostly incorporated into the liver after fat-rich meal (Fig. 1). Therefore, CM remnants with apoB48 are of different origin from very low density lipoprotein (VLDL) remnants with apoB100, which are produced and secreted from the liver. Both of these remnant lipoproteins (RLP) in the postprandial plasma are simultaneously isolated and determined by means of an immuno-separation method (RLP-C and RLP-TG assay) [1,2]. Therefore, we have long believed that the RLP in the postprandial plasma contain CM remnants (exogenous remnants; RLP-apoB48) and VLDL remnants (endogenous remnants; RLP-apoB100) of different origin, i.e. produced in the intestine and liver, respectively. However, this hypothesis proposes the different idea that the majority of apoB48 in postprandial plasma detected as VLDL-apoB48 or RLP–apoB48 are derived from the liver with VLDL-apoB100 as newly reconstructed VLDL from CM remnants, not from the intestine directly. To understand the role of RLP, it is important to clarify the characteristics of postprandial remnants if there exist really two kinds of RLP with different origins as widely accepted.

2. The characteristics of VLDL remnants and CM remnants

We reported in the Hypothesis I about the role of VLDL remnants (RLP) in postprandial plasma [3]. RLP is strongly associated with the habits of daily life, such as the kind of foods taken and frequency and strength of exercise. However, the key plasma factor which critically bridges the “fat-rich meal and the lack of exercise” and “obesity and insulin resistance” has not been established. We hypothesized that RLP may be the bridge between life style factors and metabolic disorders, which is originally based on the reconstructed VLDL in the liver from the CM remnants after fat-rich meal intake in order to distribute the energy source into the whole body. Since it has been shown that the formation of VLDL remnants after food intake can be controlled by appropriate food intake and exercise [3], the following atherosclerotic diseases may be most effectively prevented by changing the life style so as to reduce VLDL remnant formation. As we proposed that VLDL remnants are prior to the manifestation of insulin resistance in the metabolic domino [3], VLDL remnants would be a more important target for the prevention of atherosclerotic diseases than LDL-C, which cannot be reduced easily by exercise or food intake [4]. When the elevated VLDL remnants in plasma continue, the insulin resistance is induced associated with visceral obesity and accelerate the initiation

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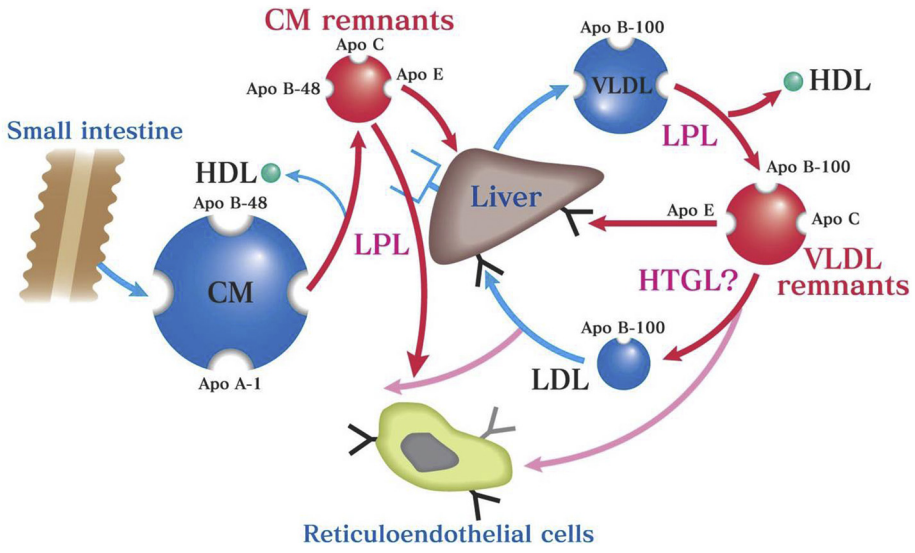

Fig. 1. Metabolic map of lipoproteins.
After fat intake, the intestine secretes chylomicrons (CM), the triglycerides of which are lipolyzed by lipoprotein lipase (LPL). The LPL reaction constitutes the initial process in the formation of triglyceride-rich lipoprotein (TRL) remnants (CM remnants and VLDL remnants). The VLDL secretion process is partly regulated by the rate of FFA influx into the liver. VLDL triglycerides are lipolyzed by endothelial-bound lipoprotein lipase, and VLDL remnant particles are formed. The final TRL remnant composition is 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. The great majority of the remnants are removed from plasma by receptor-mediated processes and the principal receptors are the LDL receptor and the LDL-receptor-related protein (LRP) in the liver. It is probable that the CM remnants use both of these routes, whereas the VLDL remnants are more likely to use only the LDL receptor.

Table 1
The changes of plasma lipids, lipoproteins and LPL concentration after fat load; Oral fat load in 54 healthy Japanese controls.
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	0 h		2 h		4 h		6 h	
	Median (25%–75%tile)		Median (25%–75%tile)		Median (25%–75%tile)		Median (25%–75%tile)	
TC (mg/dl)	225	(184–250)	230	(180–260)	230	(180–250)	230	(180–260)
TG (mg/dl)	113	(66–160)	140	(110–220)*	180	(140–380)*	160	(80–300)*
HDL-C (mg/dl)	67	(45–80)	70	(40–80)	70	(40–80)	70	(40–80)
LDL-C (mg/dl)	128	(105–150)	130	(100–150)	130	(100–140)	130	(100–150)
RLP-C (mg/dl)	5.6	(3.9–6.9)	6.3	(4.9–8.4)*	8.1	(5.4–13.8)*	7.5	(4.7–20)*
RLP-TG (mg/dl)	13.8	(5.5–29.3)	37.7	(35.4–68.4)*	86.2	(38.4–224.4)*	77.7	(16.3–142.4)*
RLP-TG/RLP-C	2.1	(1.3–4.9)	7.2	(5.7–8.5)*	11.6	(6.4–15.9)*	5.6	(3.4–11.4)*
RLP-TG/TG	0.11	(0.08–0.19)	0.32	(0.27–0.34)*	0.47	(0.31–0.59)*	0.36	(0.19–0.55)*
Apo B100 (mg/dl)	112	(89–162)	126	(88–173)	126	(95–160)	126	(101–168)
Apo B-48 (μg/ml)	6.0	(3.1–10.3)	10.8	(6.3–14)*	13.0	(6.4–18.3)*	9.3	(3.8–22.8)*
LPL (ng/ml)	71	(58–77)	69	(56–84)	62	(54–69)	67	(51–78)
LPL/RLP-TG	5.07	(2.65–10.6)	1.81	(1.60–2.01)*	0.72	(0.31–1.42)*	0.85	(0.52–3.19)*

0 h vs 2 h, 4 h, 6 h by Dun test.
* $P < 0.05$.Modified from Ref. [13].

and progression of various atherosclerotic diseases. Therefore, the role of VLDL remnants may be more important than any other lipoproteins as the bridge between life style factors and metabolic disorders.

We reconsidered the role of CM remnants with apoB48 which are derived from the fat-rich meal and are commonly believed to be the major postprandial remnants. It has become clear that most CM remnants are incorporated into the liver after fat intake within a short time after entering into the blood circulation (Fig. 1). The half-life of CM or CM remnants after intravenous injection is reported to be 5–13 min in normal controls [5,6]. However, hepatectomized dogs and rats display significantly delayed clearance of CM remnants from the circulation after fat or CM ingestion [7,8]. This means the liver plays the major role in clearing CM remnants with apoB48 from the circulation. Coincidentally, the postprandial plasma apoB48 increases in 2-4 h after fat load, with the same timing as TG, RLP-C and RLP-TG (Table 1). We reported previously that plasma TG that is increased after a fat load is mainly composed of VLDL remnants (RLP-apoB100), not CM remnants (RLP-apoB48) [9,10]. HPLC analysis also showed that the particle size of postprandial RLP-apoB48 is similar to that of RLP apoB100 [9–11]. Those results prompt us to hypothesize that apoB48 incorporated into liver as CM remnants may be reconstituted in VLDL as a portion of VLDL to form VLDL remnants after fat intake.

3. Currently accepted concepts regarding CM remnants in the postprandial plasma

Although CM remnants are cleared from the blood circulation with a very short half-life, it takes considerable time to reconstruct CM in the intestine from digested long-chain fatty acid triglycerides (LCT) after fat intake. Because of hydrophobicity of LCT, the formation of CM is necessary in order to distribute LCT in circulation from lymph duct. Therefore, the increase of apoB48 in the postprandial plasma is delayed in 2–4 h after a fat intake, which is very similar to the timing of the increase in VLDL apoB100 and their remnants in circulation. However, certain fatty acids, such as medium chain triglycerides (MCT) and diacylglycerol (DG), do not significantly increase the plasma TG or RLP-TG, because MCT and DG barely form CM in the intestine, but instead are absorbed in the intestine and smoothly incorporated into the liver via the portal vein because of its hydrophilic property [12,13].

Therefore, these results suggest that the CM remnants that are formed originally in the intestine by the LCT increased in circulation in several hours after fat intake, coincidentally similar timing with VLDL remnants. Another point is the presence of small sized apoB48 particles in the postprandial plasma. Those particles are usually recognized as small CM remnants. Therefore, VLDL or IDL size apoB48-carrying particles are believed to be the hydrolyzed CM remnants. These particles are found in the circulation in parallel with VLDL remnants after fat

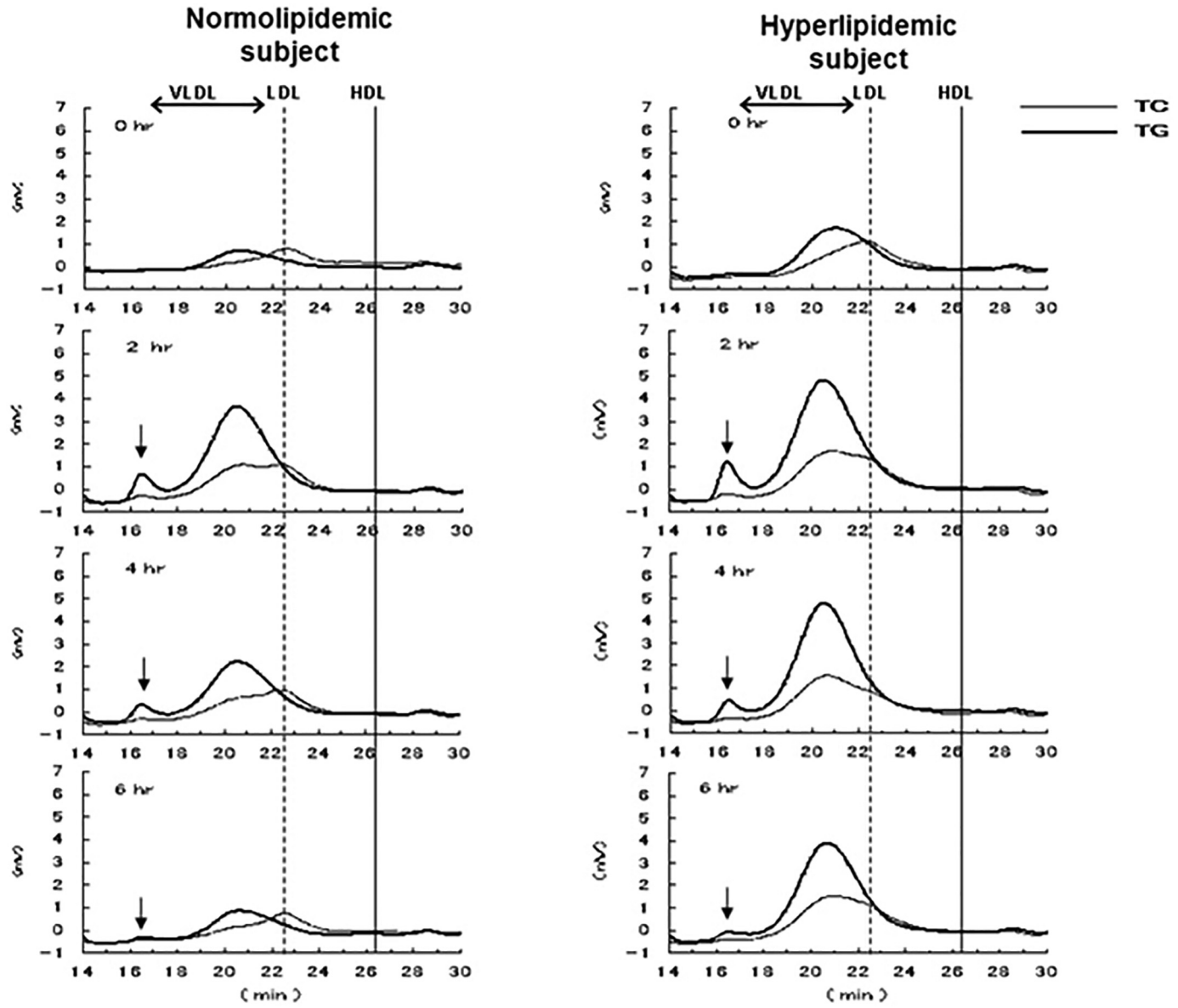

Fig. 2. HPLC profiles of RLP after a fat load (0, 2 h, 4 h and 6 h) monitored by TC and TG in a normal control and a hyperlipidemic patient.
The major lipoprotein fractions in RLP after fat load were found to have a VLDL particle size in both normal controls and hyperlipidemia patients.

intake without being incorporated into the liver. These concepts seem to be well accepted and the one we have long believed. However, the relationship between small CM remnants and VLDL1, VLDL2 and their remnants produced in the liver [14–18] has not been well elucidated.

4. VLDL apoB48 remnant hypothesis

This hypothesis was conceived because of the high concordance of the postprandial increase and decrease in apoB 48 and apoB100 in VLDL and RLP throughout the course of our many fat loading tests.

It is well known that apoB48 in humans is not synthesized in the liver, unlike mice and rats [19]. Therefore, the protein synthesis of apoB48 in the liver after fat intake does not occur in humans. 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 and LDL-receptor-related protein (LRP) [20]. Subsequently, apoB48 may be reconstituted in VLDL as VLDL apoB48 by a physiological pathway similar to that of VLDL apoB100 formation [21] and secreted into the circulation as VLDL1, 2 apoB48 and their remnants [22]. If CM is barely synthesized in the intestine by MCT and DG, VLDL apoB48 would not be produced or increased in the circulation after those fat intake [12,13]. These results suggest that apoB48 is a ligand of CM remnants essentially cleared by the liver. Therefore, VLDL apoB48 is reconstituted in the liver and fluctuates in parallel with TG and VLDL apoB100 (RLP) in the postprandial plasma for the formation of VLDL remnants (Table 1, Fig. 2). Those lipoprotein profiles after fat intake display unexpected concordance. Therefore, most CM remnants are incorporated into the liver and reappear in plasma in a small pool of soluble lipoproteins as VLDL apoB48 in the form of VLDL1 and VLDL 2 (Fig. 3). Although we don't yet know the precise mechanism of this physiological pathway for the formation of VLDL apoB48, most of the apoB48 particles in the postprandial plasma are found in the VLDL1 and 2 fractions, which are recognized as being produced in the liver, and identified as VLDL by ultracentrifugation separation (Table 2) [17–19,22] and particle size by HPLC [10,11].

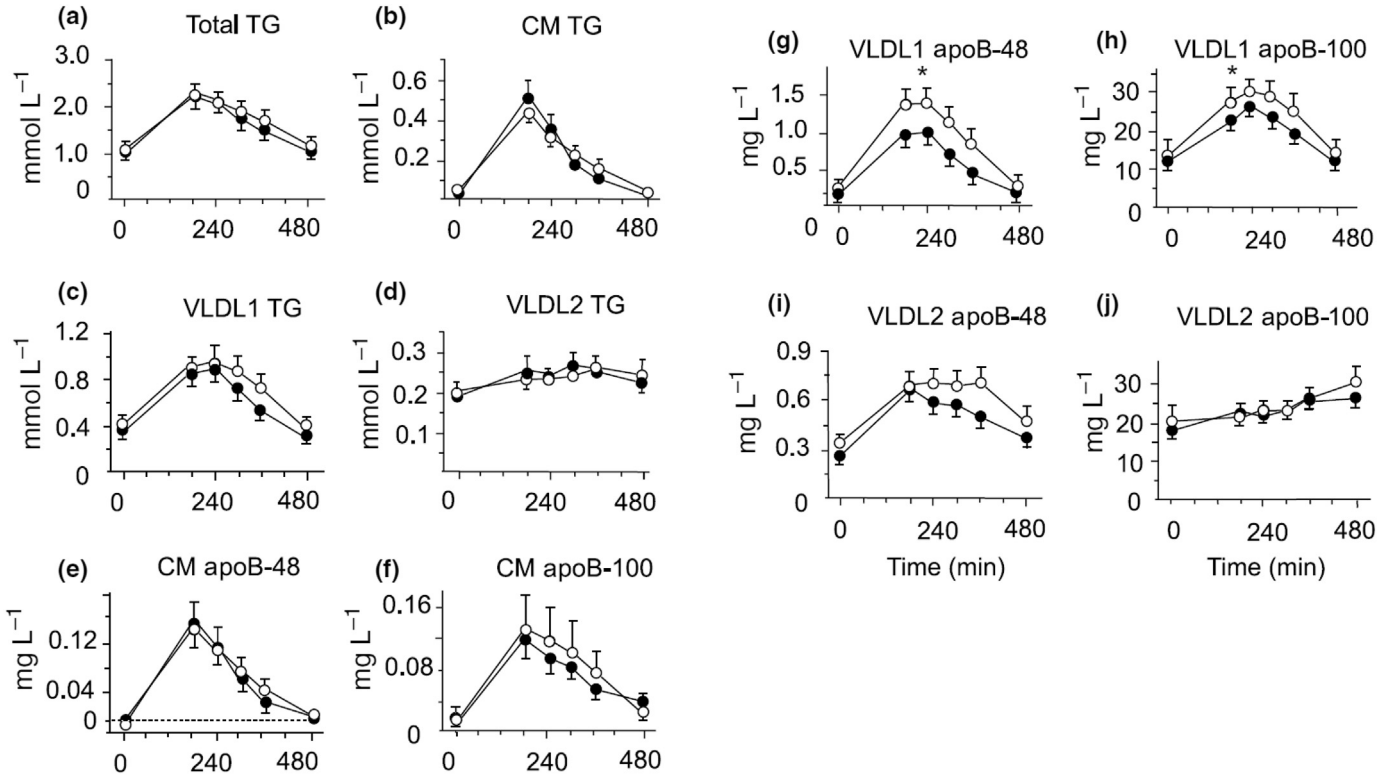

Fig. 3. Triglycerides, apolipoproteins and VLDL size during the meal tolerance test.
The total TG concentration (a), TG concentration in the CM fraction (b), TG concentration in the VLDL1 fraction (c), TG concentration in the VLDL2 fraction (d), concentration of triglyceride-rich lipoproteins (TRLs) from the intestine (apoB-48) and liver (apoB-100) in the CM fraction (e, f) concentration of TRL from the intestine and liver in the VLDL1 fraction (g, h), concentration of TRL from the intestine and liver in the VLDL2 fraction (i, j) in men with heredity type 2 diabetes (white circles) and controls (black circles), during a meal tolerance test. *AUC, $P < 0.05$.

Table 2
Postprandial response of triglycerides, apoB-48 and apoB-100 in plasma, CM, VLDL1 and VLDL2 fraction.
Johanson et al. J Intern Med, 255 (2004) 273–279

	AUC	
	Relatives	Controls
Total triglycerides[a]	853 ± 60	816 ± 53
TG Cm[a]	105 ± 9	109 ± 16
TG VLDL1[a]	356 ± 40	315 ± 33
TG VLDL2[a]	98 ± 7	101 ± 6
ApoB-48 CM[b]	34 ± 5	32 ± 7
ApoB-100 CM[b]	39 ± 13	35 ± 7
ApoB-48 VLDL1[b]	446 ± 65*	299 ± 42
ApoB-100 VLDL1[b]	11317 ± 1479*	9366 ± 971
ApoB-48 VLDL2[b]	292 ± 31	243 ± 28
ApoB-100 VLDL2[b]	11349 ± 1084	11018 ± 860

CM, chylomicrons; VLDL, very low density lipoproteins; AUC, area under the curve; TG, triglycerides.
* $P < 0.05$.
[a] mmol L^{-1} min.
[b] mg L^{-1} min.

Table 3
Kinetic parameters of apoB-48 in TRL and apoB-100 in VLDL following supplementation with n-3 PUFA in patients with type 2 diabetes.
(Tremblay AJ et al. *J Diabetes Res*. 2016)

	Placebo ($n = 10$)	n-3 PUFA ($n = 10$)	%Δ	*P*
TRL apoB-48				
Pool size, mg	99 ± 62	96 ± 62	−2.6	0.9
Fractional catabolic rate, pools/day	6.9 ± 3.8	7.6 ± 2.8	10	0.3
Production rate, mg/kg/day	5.4 ± 3.2	6.0 ± 3.8	11.1	0.7
VLDL apoB-100				
Pool size, mg	600 ± 258	594 ± 321	−0.9	0.9
Fractional catabolic rate, pools/day	6.9 ± 2.3	6.9 ± 2.4	–	0.9
Production rate, mg/kg/day	35.6 ± 12.6	33.9 ± 12.4	−5.6	0.6

PUFA: polyunsaturated fatty acid.
TRL: triglyceride-rich lipoproteins.
Mean ± SD; %Δ represents the percentage of difference between the two intervention phases.

5. Support for the hypothesis

Our hypothesis is supported by the research of Johanson el al. [22]. They employed an 8-h meal tolerance test (919 kcal, 51 g fat) during which lipoproteins were separated by density gradient ultracentrifugation [14,15]. They separated the TG-rich lipoproteins such as CM apoB48 and CM apoB100, VLDL1 apoB100 and VLDL1 apoB-48, and VLDL2 apoB100 and VLDL2 apoB48. ApoB-48 and apoB-100 were found in all of the fractions, which were separated by Svedberg flotation (Sf) rate ultracentrifugation [22]. As shown in AUC analysis after fat rich meal in Table 2, the CM apoB48 and CM apoB100 concentrations were very low and VLDL 1 apoB48 and VLDL1 apoB100 were the highest after meal intake. A similar trend was observed for VLDL2, which is a smaller VLDL with a much higher apoB48 concentration than CM apoB48 after meal intake. These results suggest that apoB48 is mostly present in the VLDL fraction after fat meal intake, while a small amount of CM apoB48 remains in the circulation during an 8 h period after meal intake, as shown in Figs. 3. Johanson el al. reported that elevated VLDL1- TRL in the postprandial state is a potentially atherogenic trait before any changes in fasting lipid

parameters, body composition or lifestyle are detectable, and may well contribute to the excess risk of future coronary events [22]. Those clinical results are very similar to those reported for RLP as a risk factor for atherosclerosis [3,10,23]. From this study, we recognized that they still defined VLDL1 apoB48 as the origin of CM remnants because of the presence of apoB48 in VLDL.

However, CM apoB48 was shown to comprise approximately 1/10 of VLDL1 apoB48 after meal intake by AUC analysis(Table 2)as we previously reported [9]. The very low concentration of CM apoB48 as AUC value means that most of the CM apoB48 was incorporated into the liver and reconstituted into VLDL1, 2 apoB48 associated with the very short half-life of CM remnants in circulation [5,6]. The AUC values for ApoB-48 VLDL1 and ApoB-100 VLDL1 in Table 2 clearly showed the highest parallel values of apoB48 and apoB100 in VLDL after fat load. Those particles are named “large VLDL” and known as a major component of VLDL remnants [9,10]. As VLDL1 apoB48 and VLDL2 apoB48 are found in the same fraction of VLDL1 apoB100 and VLDL2 apoB100 with significant concordance, as shown in Fig. 3, most of the VLDL1 apoB48 (comparable to RLP-apoB48) can be categorized as VLDL remnants, in spite of carrying CM originated apoB48. If VLDL1 apoB48 and VLDL2 apoB48, which comprise the major portion of apoB48 in the circulation, are recognized as hydrolyzed small size CM remnants, the majority of CM remnants are not incorporated into liver and remain in circulation. Furthermore, the profiles of increase and decrease of VLDL apoB48 after meal intake is surprisingly close to the profiles of VLDL remnants, in spite of the different origin sites and secretion mechanisms.

Furthermore, Tremblay et al. [24–26] reported in vivo kinetics of the TG-rich lipoprotein (TRL) apoB-48 and VLDL apoB-100 using a primed-constant infusion of L-[5,5,5-D3] leucine for 12 h in a fed state with different kind of clinical studies. For example, compared with the placebo, n-3 PUFA supplementation significantly reduced TG concentrations. However, 8-week supplementation with n-3 PUFAs in men with type 2 diabetes had no different effect on TRL apoB-48 and VLDL apoB-100 levels or kinetics. They further reported in vivo kinetic studies of TRL apoB-48 and VLDL apoB-100 in humans with medium chain triglyceride intake [25], fenofibrate and atorvastatin [26] and ezetimibe [27] treatment. From those studies, the catabolic rate (FCR) of TRL apoB48 and VLDL apoB100 was specifically similar and consistent in both normal controls and the diabetic patients (Table 3), although the production rate (PR) and pool size (PS) were significantly different between TRL apoB48 and VLDL apoB100 kinetics by the different treatment in those studies. Those results may suggest the possibility that TRL apoB48 and VLDL-apoB100 cleared from the circulation with very similar manner, because those particles have similar characteristics of lipoprotein formation in liver.

6. Testing the hypothesis and conclusions

It has been a long time question for us that the fluctuating profiles of apoB48 in RLP after fat intake are always synchronized with apoB100 in RLP in spite of the different origin and secretion site in the fat loading studies during many years. Therefore, we hypothesized that CM apoB48 after fat intake in humans is reconstituted or remodeled in the liver as VLDL apoB48 along with the VLDL apoB100 formation pathway after incorporated from the circulation, unlike mice and rats which can synthesize apoB48 in the liver. In order to prove this hypothesis, it is necessary to clarify the new pathway underlying the incorporation of apoB48 into VLDL particles in the liver after fat intake. If clarified the new pathway of VLDL apoB48 formation, the remnant lipoproteins isolated by an immuno-separation method as “RLP apoB48” could be defined as VLDL remnants, not CM remnants, because those particles are newly reconstituted in the liver as a portion of VLDL. Therefore, we hypothesize that RLP-apoB100 and RLP-apoB48 are both endogenous VLDL remnants produced in the liver after food intake, completely remodeled from the food component to metabolic factor as a bridge of metabolism. Majority of CM remnants after fat intake are metabolized in liver, reconstructed into VLDL remnants and are provided to heart, muscles, adipocytes, endothelium, etc. as an energy supply lipoproteins similar to blood sugar. However, VLDL remnants play the role for the major initiator of the metabolic domino effect to cardiovascular diseases when supplied excessively and continuously [3,10].

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