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Formation of preβ1-HDL during lipolysis of triglyceride-rich lipoprotein

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ABSTRACT

Preβ1-HDL, a putative discoid-shaped high-density lipoprotein (HDL) is known to participate in the retrieval of cholesterol from peripheral tissues. In this study, to clarify potential sources of this lipoprotein, we conducted heparin injection on four Japanese volunteer men and found that serum triglyceride (TG) level decreased in parallel with the increase in serum nonesterified fatty acids and plasma lipoprotein lipase (LPL) protein mass after heparin injection. Plasma preβ1-HDL showed considerable increases at 15 min after the heparin injection in all of the subjects. In contrast, serum HDL-C levels did not change. Gel filtration with fast protein liquid chromatography system (FPLC) study on lipoprotein profile revealed that in post-heparin plasma, low-density lipoprotein and αHDL fractions did not change, whereas there was a considerable decrease in very low-density lipoprotein (VLDL) fraction and an increase in preβ1-HDL fraction when compared with those in pre-heparin plasma.

We also conducted *in vitro* analysis on whether preβ1-HDL was produced during VLDL lipolysis by LPL. One hundred microliters of VLDL extracted from pooled serum by ultracentrifugation was incubated with purified bovine milk LPL at 37 °C for 0–120 min. Preβ1-HDL concentration increased in a dose dependent manner with increased concentration of added LPL in the reaction mixture and with increased incubation time, indicating that preβ1-HDL was produced during lipolysis of VLDL by LPL.

Taken these *in vivo* and *in vitro* analysis together, we suggest that lipolysis of VLDL particle by LPL is an important source for formation of preβ1-HDL.

Preβ1-HDL, a putative discoid-shaped HDL of approximately 67 kDa mass that migrates with preβ mobility on agarose gel electrophoresis, contains apolipoprotein A-I (apoA-I), phospholipids, and unesterified cholesterol. Preβ1-HDL plays an important role in reverse cholesterol transport, although it comprises only 1–5% of total apoA-I in blood plasma. The initial step of reverse cholesterol transport, called cholesterol efflux, is a reaction by which excessively accumulated cholesterol in peripheral tissues is retrieved by HDL. Preβ1-HDL is known as the initial plasma acceptor of cell-derived cholesterol [1–3].

Although preβ1-HDL has been observed both in plasma [1–3] and peripheral lymph [4], the origin and metabolic fate remain obscure. There are four potential sources of preβ1-HDL (lipid-poor apo A-1) in plasma: (1) it may be released as lipid-poor protein after its synthesis in the liver and intestine [5–7]; (2) it may be generated within the plasma during the remodeling of mature, spherical HDL particles [8,9]; (3) it may be generated through interaction of apoA-I and ATP-binding cassette transporter A1 (ABCA1) located on peripheral cell membranes [10–12]; (4) it may be released from triglyceride (TG)-rich lipoproteins that are undergoing hydrolysis by lipoprotein lipase (LPL) [13]. For the possibility of (4), TG-rich lipoproteins have been reported to be the source of significant amount of the apo A-1 in plasma [14,15] and apo A-1 in TG-rich lipoproteins has been shown to be a precursor of the pool of apo A-1 in HDL [16,17]. However, it is not known whether preβ1-HDL is directly released from TG-rich lipoproteins by lipolysis.

Several methods have been developed for measuring plasma preβ1-HDL, i.e., a native two-dimensional gel electrophoresis [1], an ultrafiltration-isotope dilution technique [18], a high-performance size-exclusion chromatography [19] and a sandwich enzyme immunoassay (EIA) we previously reported, which uses a monoclonal antibody (Mab55201) specifically recognizing an

Abbreviations: HDL, high-density lipoprotein; CHO, cholesterol; TG, triglyceride; NEFA, nonesterified fatty acids; FPLC, fast protein liquid chromatography; LPL, lipoprotein lipase; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein; apoA-I, apolipoprotein A-I.

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epitope of apo A-I that is exposed only in preβ1-HDL [20]. The EIA kits are now commercially available (Sekisui Medical Co., Ltd., Tokyo, Japan). Since then, the measurement of preβ1-HDL in plasma became much easier and numerous studies were conducted on the metabolism of this lipoprotein.

In this background, to clarify possible sources of preβ1-HDL, we investigated correlation between LPL concentration and preβ1-HDL in plasma after heparin injection in four volunteer Japanese men. We also conducted *in vitro* analysis on formation of preβ1-HDL by incubating VLDL with purified bovine milk LPL.

Materials and methods

Four volunteer Japanese men were involved in this study (Table 1). They were fasted for at least 12 h, injected heparin (30 IU/kg) intravenously and blood sampling was conducted at 0, 15 and 30 min after the injection. Blood was collected into tubes containing EDTA-2Na as the anticoagulant and chilled on ice water immediately after blood drawing. Blood was then centrifuged at 4 °C, 2000 rpm for 30 min to isolate plasma. The plasma for measuring preβ1-HDL was diluted with 20 volumes of 50% sucrose solution for stabilization and then stored at −80 °C until preβ1-HDL was assayed [21]. Plasma lipid concentrations were measured by enzymatic method. Apolipoprotein concentrations were measured by turbidimetric assay.

Table 1
Baseline characteristics of study subjects.

	Subjects				Mean	SD
	1	2	3	4		
Age (years)	46	45	44	32	41.8	6.6
BMI (kg/m^2)	24.0	22.6	32.2	22.1	25.2	4.7
CHO (mg/dl)	209	180	247	157	198	39
LDL-C (mg/dl)	133	103	179	51	117	54
HDL-C (mg/dl)	54	56	46	92	62.0	20.5
TG (mg/dl)	115	123	211	50	125	66
ApoA-I (mg/dl)	142	155	128	187	153	25
Preβ1-HDL (μg/ml)	27.3	36.7	28.1	27.6	29.9	4.5
LPL (ng/ml)	34.9	40.9	27.6	46.4	37.5	8.1
NEFA(μEq/L)	710	1087	1020	568	846	248

CHO, total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglycerides; LPL, lipoprotein lipase; NEFA, nonesterified free fatty acid.

Measurement of plasma preβ1-HDL was conducted as previously reported [20,21], with the sandwich enzyme immunoassay (EIA) using mouse anti-human preβ1-HDL monoclonal antibody (MAb 55201) and goat anti-human apoA-I polyclonal antibody. LPL mass was measured by a sandwich enzyme immunoassay as previously reported [22].

Gel filtration analysis for lipoprotein was conducted using Pharmacia fast protein liquid chromatography (FPLC) system composed of a Superose 6 HR 10/30, a Superdex 200 HR 10/30 and two Superose 12 HR 10/30 columns (GE Healthcare). Two hundred microliters of pre-heparin or post-heparin (15 min after injection) plasma taken from subject 3 was loaded to the system. The system was run with 0.9% NaCl solution at a flow rate of 0.15 ml/min and fractionation was started after 180 min with 0.6 ml per fraction. Fractions 1–80 containing the separated lipoproteins were used to determine CHO, TG and preβ1-HDL levels of each fraction.

To clarify whether preβ1-HDL was produced during the process of lipolysis of TG-rich lipoproteins *in vitro*, we measured preβ1-HDL concentration in the reaction mixture before and after incubating VLDL with purified bovine milk LPL. VLDL ($d < 1.006$) was obtained by ultracentrifugation of pooled fresh serum taken from healthy volunteers. The reaction was conducted with 100 μl of

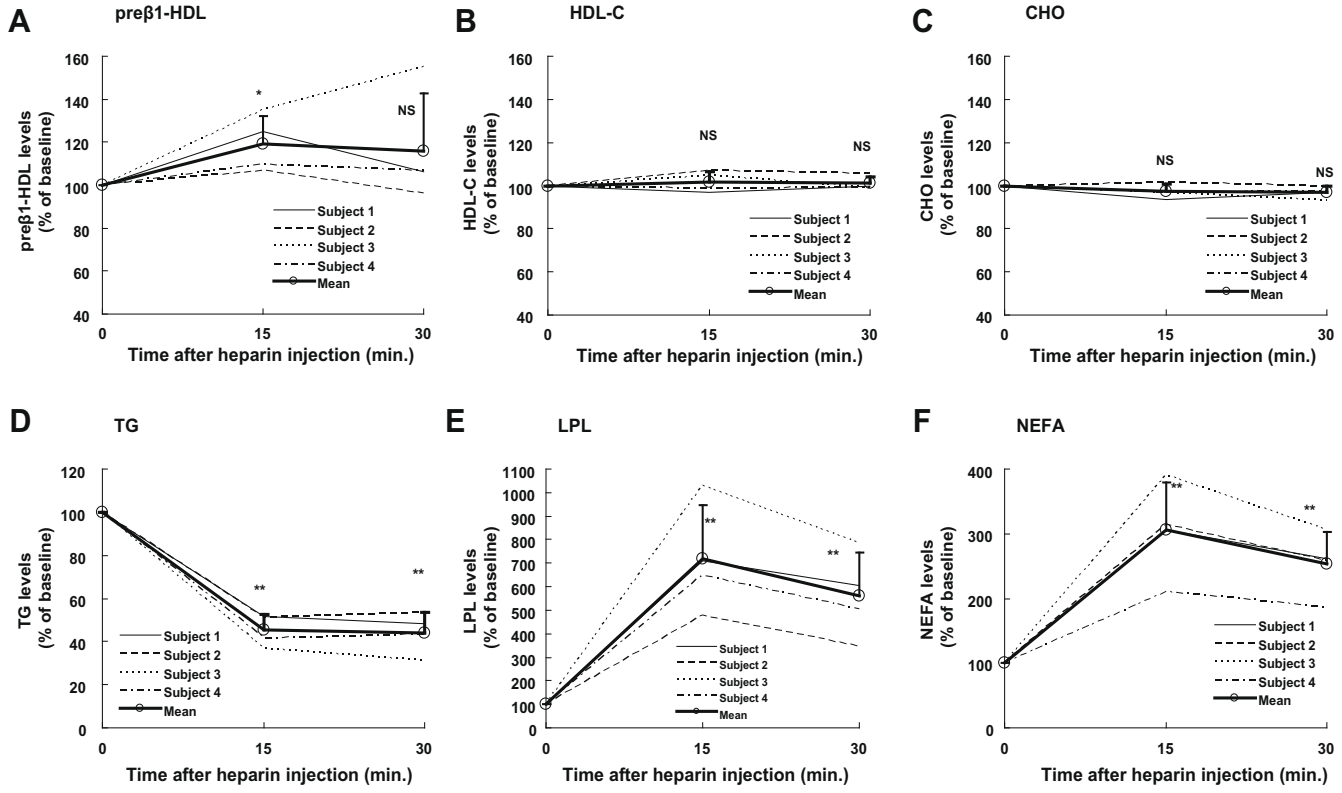

Fig. 1. Changes in plasma preβ1-HDL and other lipid marker levels after heparin injection. (A) preβ1-HDL; (B) HDL-C; (C) CHO; (D) TG; (E) LPL; (F) NEFA. Values are expressed as % of baseline (pre-heparin) of each subject or mean of four subjects. Error bars of the mean values represent standard deviations of four subjects. NS, no statistical significance versus baseline; *$P < 0.05$ versus baseline; **$P < 0.01$ versus baseline.

VLDL (CHO: 99.4 mg/dl, TG: 434 mg/dl) and 100 μl of purified bovine milk LPL (Sigma) (final concentration, 0–20 μg/ml) at 37 °C for 0–120 min with PBS. After the reaction, the mixture was placed on ice water and NEFA and preβ1-HDL concentrations were measured.

The study protocol was approved by the institutional review board of Chiba University Medical School (J.K. used to belong to Chiba University (see Ref. [20]) and this study was conducted during that period). All participants gave informed consent.

Statistical analyses were performed using Stat Flex for Windows ver. 5.0 (Artech Inc., Osaka, Japan). The difference between two values was assessed using Student's paired *t*-test. For all analyses, $P < 0.05$ was considered statistically significant.

Results

Changes in plasma preβ1-HDL concentration after heparin injection

Changes in preβ1-HDL and other parameters related to lipoprotein metabolism before and after heparin injection

Fig. 1 shows plasma preβ1-HDL, HDL-C, CHO, TG, LPL and NEFA levels before and after heparin injection. Plasma preβ1-HDL level markedly increased at 15 min, whereas HDL-C level did not change at all (Fig. 1A and B). The increase in preβ1-HDL level was significant at 15 min, but not at 30 min. The preβ1-HDL levels of three normolipidemic subjects returned to baseline levels at 30 min, whereas the level of the subject 3 with hyperlipidemia showed further elevation at 30 min (Fig. 1A). Plasma TG level decreased in parallel with increases in plasma NEFA and LPL protein mass after heparin injection. In contrast, plasma CHO level did not change (Fig. 1C–F).

FPLC analysis of plasma lipoprotein before and after heparin injection

FPLC analysis was performed for plasma before and 15 min after the heparin injection from the subjects 3, who showed the most pronounced preβ1-HDL elevation at 15 min after heparin injection. Each lipoprotein fraction was monitored by CHO, TG and preβ1-HDL concentrations. As shown in Fig. 2, VLDL fraction decreased, whereas preβ1-HDL increased considerably in plasma at 15 min after heparin injection compared with those fractions in pre-heparin plasma. In contrast, LDL and αHDL fractions were almost unchanged.

In vitro analysis on VLDL hydrolysis by LPL, causing the production of preβ1-HDL

VLDL extracted from pooled serum by ultracentrifugation was incubated with bovine milk LPL at 37 °C for 0–120 min. Reaction mixture was placed on ice water immediately after the incubation to stop the reaction and NEFA and preβ1-HDL concentrations in the reaction mixture were measured. Preβ1-HDL and NEFA concentrations increased in parallel with increased concentration in added LPL in the reaction mixture (Fig. 3A). We also investigated the effect of incubation time-course on the production of NEFA and preβ1-HDL in the reaction mixture and found that the produced preβ1-HDL concentration in the reaction mixture increased as was the longer the incubation time (Fig. 3B). These results indicate that preβ1-HDL was produced during the process of lipolysis of VLDL by the added LPL.

Discussion

The major findings of this study were as follows: (1) plasma TG level decreased in parallel with the increases in serum NEFA and plasma LPL mass at 15 and 30 min after heparin injection. Plasma preβ1-HDL level showed considerable increase at 15 min after the heparin injection. (2) FPLC analysis showed that VLDL fraction decreased, whereas preβ1-HDL fraction increased in post-heparin plasma when compared with those fractions in pre-heparin plasma, and its molecular weight was identical with the preβ1-HDL originally existed in plasma before heparin injection. (3) *In vitro* analysis on VLDL hydrolysis by LPL showed that preβ1-HDL concentration increased in parallel with increased concentration of added LPL in the reaction mixture and with increased incubation time. These findings suggest that preβ1-HDL was newly produced during lipolysis of TG-rich lipoprotein of by LPL.

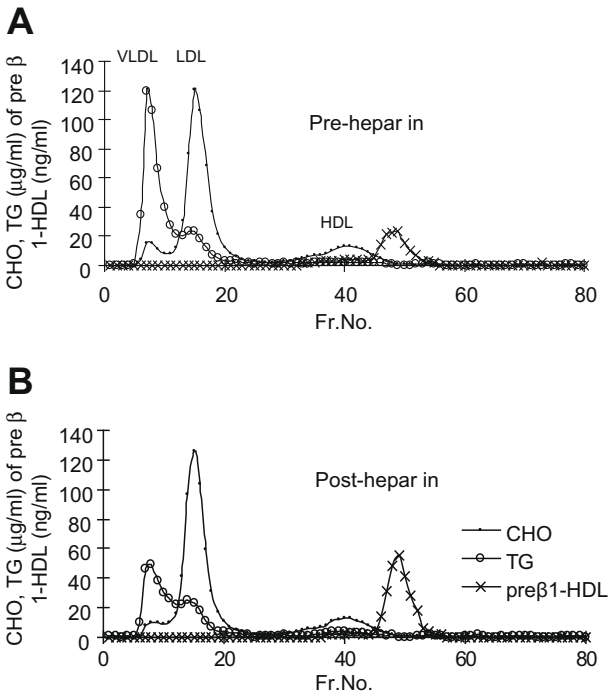

Fig. 2. FPLC analysis of plasma cholesterol, triglyceride and preβ1-HDL distributions in pre-heparin (A) and post-heparin (B) plasma.

Neary et al. reported that preβ-HDL was produced from TG-rich lipoproteins by lipolysis, *in vivo* and *in vitro* [23]. At first glance, their findings seem compatible with our present results. However, preβ-HDL in their study is distinct from preβ1-HDL in that the former contains various heterogeneous particles, including structurally and physiologically different preβ2-HDL and preβ3-HDL from preβ1-HDL [1–3]. In addition, for clinical aspects in human plasma level, preβ-HDL is known to be different from preβ1-HDL, i.e. in subjects with coronary heart disease preβ-HDL is reported to be markedly decreased [24], whereas preβ1-HDL is markedly increased [25,26]. Thus, we conclude that our present findings on preβ1-HDL are not the ones confirming their results focusing on preβ-HDL. In the present study we clearly showed for the first time that preβ1-HDL was generated during lipolysis of TG-rich lipoproteins, using the immunoassay we previously developed [20].

Other potential mechanism of preβ1-HDL being newly produced might be lipolysis of large HDL by hepatic triglyceride lipase (HTGL), since HTGL is another lipase to be released into plasma by heparin injection. Barrans et al. [27] showed that preβ1-HDL was generated from human TG-enriched HDL_2 after a 120-min incubation with rat HTGL. However, the present finding in the FPLC study did not show a significant change in αHDL between before and after heparin injection, suggesting that HTGL-related conversion of HDL_2 particle to smaller HDL particle is not likely to contribute highly to the formation of preβ1-HDL after heparin injection. Indeed, Miida et al. [28] have reported that preβ1-HDL was increased in individuals with high TG, being compatible with our present finding in this respect, but failed to find a positive correlation be-

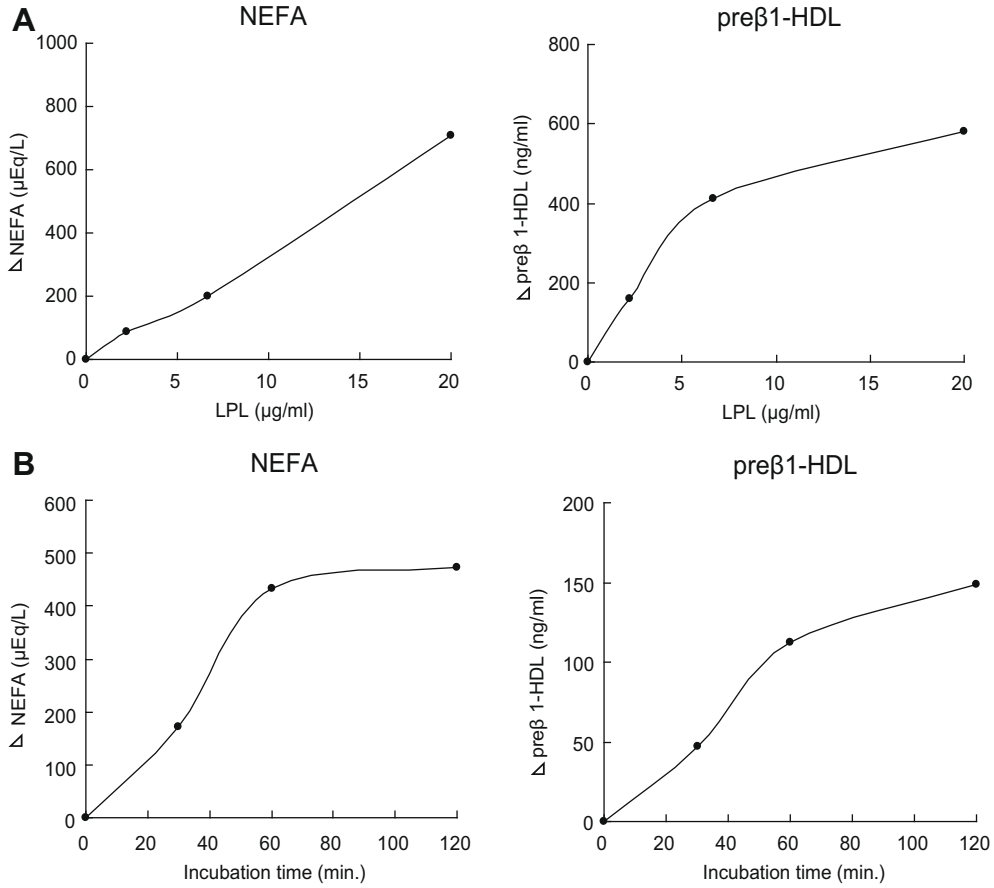

Fig. 3. *In vitro* production of preβ1-HDL on VLDL hydrolysis by LPL. (A) Relation between preβ1-HDL increase and added LPL amount (final LPL concentration, 0–20 μg/ml; incubation time, 60 min). (B) Relation between preβ1-HDL increase and incubation time (final LPL concentration, 20 μg/ml; incubation time, 0–120 min). Left and right panels show increase in NEFA and preβ1-HDL levels, respectively. Data points represent means in duplicate.

tween the change in preβ1-HDL and that in HTGL activity after bezafibrate treatment. This suggests that mechanisms other than HTGL activity might be highly involved in the formation of preβ1-HDL in hypertriglyceridemia after bezafibrate treatment in their study.

Limitations of this study need to be mentioned. We did not conduct activity assay for LPL or HTGL. If we had done, we might have been able to show additional mechanism involved in the production of preβ1-HDL from the standpoint of lipolytic enzymes. However, as mentioned above, HTGL is unlikely a major determinant of the production of preβ1-HDL [28]. On the other hand, one of the strong points of our study is in that we showed both *in vivo* and *in vitro* evidence of LPL being highly involved in the production of preβ1-HDL.

Aside from lipolysis of TG-rich lipoprotein by lipolytic enzymes, several other mechanisms for the formation of preβ1-HDL have been proposed or demonstrated in the literatures. For example (1) preβ1-HDL may be released as lipid-poor protein after its synthesis in the liver and intestine [5–7]; (2) preβ1-HDL may be generated within the plasma during the remodeling of mature, spherical HDL particles [8,9]; (3) it may be generated through interaction of apoA-I and ATP-binding cassette transporter A1 (ABCA1) located on peripheral cell membranes [10–12]. Very recently, an apolipoprotein A-I mimetic is reported to dose-dependently increase the formation of preβ1-HDL in human plasma [29].

Another finding of this study is that the hyperlipidemic subject showed further elevation of preβ1-HDL level at 30 min after heparin injection, whereas three normolipidemic subjects showed reduced preβ1-HDL levels to the baseline levels at 30 min. We speculate two potential mechanisms for this result. One possible mechanism is that the production of preβ1-HDL from TG-rich lipoproteins by lipolysis may continue until 30 min after heparin injection in the hyperlipidemic subject since absolute amount of TG-rich lipoproteins in plasma was high. Another possible mechanism is that catabolism of preβ1-HDL is delayed in the hyperlipidemic subject compared with other normolipidemic subjects. As the catabolic pathway of preβ1-HDL, lecithin-cholesterol acyltransferase (LCAT)-dependent conversion pathway has been suggested to exist [30,31]. Miida et al. reported that LCAT-dependent conversion rate is a determinant of plasma preβ1-HDL concentration in healthy Japanese [32] and that delayed LCAT-depending conversion of preβ1-HDL into α-migrating HDL is responsible for elevation of plasma preβ1-HDL levels in hemodialysis patients [33] and in coronary artery disease [25]. The same could have occured in the hyperlipidemia subject although we regrettably did not determine the LCAT-dependent conversion rate or LCAT activity in the plasma samples in this study.

In summary, we showed for the first time the evidence that preβ1-HDL particle was generated during lipolysis of TG-rich lipoproteins by LPL.

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