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Review

Hypothesis: Postprandial remnant lipoproteins are the causal factors that induce the insulin resistance associated with obesity

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ABSTRACT

We have long thought that remnant lipoproteins (RLP) in plasma are significantly increased as the result of disturbed lipoprotein metabolism followed by obesity and insulin resistance. Therefore, it was believed that insulin resistance causes and enhances RLP formation. In contrast, this hypothesis states that RLP induces insulin resistance as the result of obesity associated with the excessive fat intake. The majority of plasma TG increased after fat intake is TG in RLP (RLP-TG) and the majority of postprandial RLP is VLDL remnants, not CM remnants. RLP is newly formed lipoproteins primarily for energy supply against starvation, like blood sugar after carbohydrate intake. Since RLP bearing apoE, LPL and Lp(a) function as ligands for the VLDL receptor, RLP interacts with the VLDL receptor in visceral fat adipocytes and stored as TG similar to excessive blood sugar. However, the excessive VLDL remnants induces obesity and its associated insulin resistance, which plays a major role as the initiator of metabolic domino effects, similar to blood sugar primarily serving as an energy supply to protect against starvation.

1. Introduction

The experimental and clinical results associated with technological advances over the last three decades have shown remnant lipoproteins (RLP) to be a key causal factor in atherosclerosis [1]. Our research has focused on the postprandial RLP which, similar to blood sugar, newly formed after food intake and fluctuates significantly between fasting and after food intake. 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 have hypothesized that RLP may be the bridge between life style factors and metabolic disorders, because RLP after fat intake has very similar metabolic characteristics with blood sugar after carbohydrate intake. Although we have focused on RLP as the causal factor of atherosclerosis, we found the essential metabolic pathways required to form RLP in healthy humans after food intake to be quite strict. RLP is approximately 1/3 of the TG-rich lipoproteins formed in plasma and is increased significantly within a few hours after fat intake [1]. Therefore, we hypothesized that RLP serves as the mediator of TG supply to adipose tissue and muscles as a reserve energy source against starvation, not just a causal factor of atherosclerosis under disturbed physiological conditions. For protecting against starvation, chylomicrons (CM) and very low density lipoprotein (VLDL) are metabolized by LPL and formed somewhat activated particles so as to interact with the receptors. Therefore, RLP may be the source of TG in adipose tissue primarily for energy supply against starvation under physiological conditions. The mechanism underlying the storage of TG by blood sugar in obesity and insulin resistance has been well investigated [2], but the mechanism by which blood lipids and lipoproteins lead to the storage of TG in adipose tissue has not been established yet. Zilversmit [3] first proposed that the postprandial lipoproteins (CM and CM remnants) that are increased after food intake are a major risk factor in atherosclerosis besides familial hyperlipidemia. They are defined as a risk factor because CM and CM remnants are known to increase significantly after food intake. Following his proposal, we elucidated the characteristics of postprandial RLP by using an immunoseparation method we developed [1], especially after a fat load, which mimics fat-rich meal intake [4]. Upon analyzing the isolated RLP, Havel's lab and our own determined that VLDL remnants, not CM remnants, are the major postprandial lipoproteins, which was shown by an analysis of the apoB100 and apoB48 in RLP. [4–8]. We hypothesized that the role for the formation of VLDL remnants after food intake is to provide TG as energy supply to organs and tissues, in particular to adipose tissue to prepare against starvation. Further excessive supply of RLP from the blood stream enhances the accumulation of TG as visceral

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obesity. The adipocytes enlarged by the accumulated TG increase the secretion of TNF-α and other adipocytokines [2], and induces insulin resistance which, in turn, initiates the metabolic domino effect in various atherosclerotic diseases.

2. The currently accepted concept on the relationships among obesity, insulin resistance and postptrandial hyperlipidemia (VLDL remnants)

The following are the currently accepted concepts on the relationship between obesity, insulin resistance and postprandial hyperlipidemia. Although obesity is considered to start before insulin resistance, hyperlipidemia has been generally believed to be induced after insulin resistance. Bernard et al. [9] reported that diet-induced insulin resistance precedes other aspects of the metabolic syndrome such as obesity and hyperlipidemia. Therefore, when fed fat rich meal, insulin resistance is believed to appear first and then, postprandial hyperlipidemia (VLDL remnants) and obesity follow it. Once insulin resistance is induced, blood glucose or TG (VLDL remnants) starts to rise, initially after meals. The disorders of lipid as well as carbohydrate metabolism are known to be accelerated by insulin resistance. As insulin resistance enhances the supply of free fatty acids (FFA) from adipose tissue to the liver, TG synthesis in the liver increases and this further increases the secretion of VLDL in plasma. In plasma, as LPL located on the capillary endothelium in muscles and adipose tissue is known to be sensitive to insulin, the insulin resistance causes the decrease of LPL activity and an increase CM and VLDL remnants in plasma. Therefore, the current concepts teach us that postprandial hyperlipidemia (VLDL remnants) is the result of insulin resistance. Our hypothesis suggests a new concept that elevated plasma VLDL remnants detected by immuno-separation method [1] are present after fat rich meal prior to obesity and insulin resistance. When VLDL remnants in plasma are formed excessively and continuously, they cause obesity and insulin resistance and enhance the progression of atherosclerotic diseases on the model of a metabolic domino via mechanisms similar to excessive glucose burden.

3. The characteristics of VLDL remnants acting as the mediator of triglyceride supply to adipose tissue

CM and VLDL are known to increase significantly after fat intake along with TG. We reported that > 80% of the TG increase (postprandial TG - fasting TG) after a fat load consisting of remnant TG (RLP-TG) (Table 1). Therefore, VLDL remnants are the major lipoproteins that are newly formed right after fat intake and fluctuate significantly in the blood circulation over the course of a day, exerting various bioactive effects (1). The increased postprandial RLP-C and RLP-TG displayed a major peak at a VLDL particle size by HPLC analysis (Fig. 1), not a large chylomicron particle size (4, 6). The particle size of apoB48 bearing RLP (CM remnants) was shown to be similar or somewhat smaller than apoB100 bearing RLP (VLDL remnants) after a fat load (Fig. 2) [7]. Large particle CM seems to be metabolized by different metabolic pathway from remnant formation.

Schneeman et al. [10] reported the postprandial responses (after fat load) of apoB-48 and apoB-100 were highly correlated with those of TG-rich lipoproteins (TRL). Although the increase in apoB-48 represented a 3.5- fold difference in concentration as compared with a 1.6-fold increase in apoB-100, apoB-100 accounted for approximately 80% of the increase in the lipoprotein particles in TRL. Similar data was presented by Cohn et al. [11], suggesting that apoB-100 TRL make a significant contribution to the total plasma triglyceride concentration in the fed as well as (in the) fasted state. We also reported that the increase of apoB-100 particles in RLP is actually far greater than that of the apoB-48 particles in the postprandial plasma [4, 6] (Fig. 3).

After the reduction in the TG hydrolyzed by LPL, it is generally believed that the CM and VLDL particles become smaller remnant particles, such as intermediate density lipoproteins (IDL). However, several studies, including our own [12, 13], revealed RLP to be predominantly of large VLDL size, which may indicate an insufficient hydrolysis by LPL in response to the excessive supply of CM and VLDL on the endothelium after food intake. The large particle sized RLP remains for a longer period of time in the circulation than the smaller particle RLP, because the larger sized RLP bear a smaller amount of LPL for lipolysis and as a ligand for the receptors (13, 14).

4. Hypothesis of VLDL remnants being the initiator of obesity and insulin resistance

Since the increase of VLDL remnants in plasma is the first step of lipoprotein metabolism right after fat-rich meal intake, as in the case of blood sugar after carbohydrate-rich meal intake, we propose the hypothesis that VLDL remnants are an additional factor with a role in the storage of TG from the circulation in adipose tissue. Stanhope et al. [15] reported that dietary fructose, but not glucose, specifically initiates an increase in de novo lipogenesis, promotes dyslipidemia, increases visceral adiposity and decreases insulin sensitivity (insulin resistance) in overweight/obese adults. The consumption of fructose increases the levels of postprandial TG, RLP-C and RLP-TG before the increase of visceral adipose volume and apparent insulin resistance, whereas consumption of glucose does not. Namely, diet-induced hyperlipidemia induces obesity and its associated insulin resistance in humans as in rats [9]. Obesity is known as a key factor for the initiation of diabetes. Also medium-chain triglycerides (MCT) and diacylglycerol (DG) are known

Table 1
The changes of plasma lipids, lipoproteins and LPL concentration after fat load; Oral fat load in 54 healthy Japanese controls.

	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 * $p < .05$. Modified from Ref. 14