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Review

New and emerging regulators of intestinal lipoprotein secretion

Changting Xiao [a,b,c], Satya Dash [a,b,c], Cecilia Morgantini [a,b,c], Gary F. Lewis [a,b,c,*]

[a] Department of Medicine, University of Toronto, Canada
[b] Department of Physiology, University of Toronto, Canada
[c] Banting and Best Diabetes Centre, Toronto General Hospital, 200 Elizabeth Street, EN12-218, Toronto, Ontario M5G 2C4, Canada

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ABSTRACT

Overproduction of hepatic apoB100-containing VLDL particles has been well documented in animal models and in humans with insulin resistance such as the metabolic syndrome and type 2 diabetes, and contributes to the typical dyslipidemia of these conditions. In addition, postprandial hyperlipidemia and elevated plasma concentrations of intestinal apoB48-containing chylomicron and chylomicron remnant particles have been demonstrated in insulin resistant states. Intestinal lipoprotein production is primarily determined by the amount of fat ingested and absorbed. Until approximately 10 years ago, however, relatively little attention was paid to the role of the intestine itself in regulating the production of triglyceride-rich lipoproteins (TRL) and its dysregulation in pathological states such as insulin resistance. We and others have shown that insulin resistant animal models and humans are characterized by overproduction of intestinal apoB48-containing lipoproteins. Whereas various factors are known to regulate hepatic lipoprotein particle production, less is known about factors that regulate the production of intestinal lipoprotein particles. Monosaccharides, plasma free fatty acids (FFA), resveratrol, intestinal peptides (e.g. GLP-1 and GLP-2), and pancreatic hormones (e.g. insulin) have recently been shown to be important regulators of intestinal lipoprotein secretion. Available evidence in humans and animal models strongly supports the concept that the small intestine is not merely an absorptive organ but rather plays an active role in regulating the rate of production of chylomicrons in fed and fasting states. Metabolic signals in insulin resistance and type 2 diabetes and in some cases an aberrant intestinal response to these factors contribute to the enhanced formation and secretion of TRL. Understanding the regulation of intestinal lipoprotein production is imperative for the development of new therapeutic strategies for the prevention and treatment of dyslipidemia. Here we review recent developments in this field and present evidence that intestinal lipoprotein production is a process with metabolic plasticity and that modulation of intestinal lipoprotein secretion may be a feasible therapeutic strategy in the treatment of dyslipidemia and possibly prevention of atherosclerosis.

Contents

Abbreviations: Apo, apolipoprotein; CVD, cardiovascular diseases; DPP-4, dipeptidyl peptidase-4; FFA, free fatty acids; GIP, gastric inhibitory polypeptide; GLP-1, glucagon-like peptide-1; GLP-2, glucagon-like peptide-2; GLP-1R, GLP-1 receptor; TG, triglycerides; TRL, triglyceride-rich lipoprotein.

* Corresponding author. Toronto General Hospital, 200 Elizabeth Street, EN12-218, Toronto, Ontario M5G 2C4, Canada. Tel.: +1 416 340 4270; fax: +1 416 340 3314.
E-mail address: gary.lewis@uhn.ca (G.F. Lewis).

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1. Introduction – the typical dyslipidemia of insulin resistant states and potential atherogenicity of intestinally derived lipoprotein particles

Insulin resistant states, which include the metabolic syndrome and type 2 diabetes, are associated with accelerated atherosclerosis and clinically significant cardiovascular disease (CVD) [1]. The typical dyslipidemia of these conditions consists primarily of elevated fasting and postprandial triglyceride-rich lipoproteins (TRL; VLDL, IDL and chylomicrons), decreased HDL-c and increased small, dense LDL particles [2]. The mechanism whereby these conditions accelerate the atherosclerotic process is complex and multifactorial, with the typical dyslipidemia that accompanies these conditions playing a role in the process [3]. Non-fasting plasma triglyceride (TG) concentration is a strong predictor of cardiovascular disease risk, independent of traditional CVD risk factors [4,5]. Increased CVD risk associated with non-fasting TG may be due to the atherogenic and inflammatory properties of TRL particles generated in the postprandial state [6,7]. Partially catabolized cholesterol-rich TRL remnants have been shown to be proatherogenic [7–9]. The role of apoB48-containing lipoprotein particles in the development of atherosclerosis is increasingly being recognized. Although chylomicron particles are felt to be too large to enter the vessel wall, chylomicron remnants following lipoprotein lipase hydrolysis, are small enough for entry into the subendothelial space and contribute to the formation of atherosclerotic lesions [10]. Chylomicron remnant particles are relatively enriched in cholesterol, are chemically modified and accumulate in the subendothelial space, as do apoB100-containing remnants, and impair endothelial function [7,11,12]. ApoB48-containing TRL and remnants are elevated in type 2 diabetes [13–15] and are implicated in the impairment of endothelium-dependent vasodilator function [16]. Fasting apoB48 is associated with asymptomatic peripheral arterial disease in patients with type 2 diabetes [17], and correlates with coronary artery disease [18]. Fasting serum apoB48 is strongly correlated with postprandial lipemia and is thus proposed as a marker of postprandial lipemia [19]. Serum apoB48 levels are correlated with carotid intima-media thickness in subjects with normal serum TG levels [20]. Fasting apoB48 concentration, therefore, could serve as a useful marker for atherosclerosis risk [21] and the apoB48/TG ratio has been proposed as a marker for detecting early atherosclerosis, even when TG levels are not elevated, such as for the detection of type III hyperlipidemia after antihyperlipidemic interventions [22]. The potential atherogenicity of apoB48-containing particles goes well beyond the particle's direct role in the atherosclerotic process, in that an elevated TRL contributes to unfavorable changes to other lipoprotein particles, i.e. low HDL and increased small dense LDL, giving rise to the "atherogenic lipoprotein phenotype" [23,24].

2. Overproduction of intestinal lipoproteins in insulin resistance and type 2 diabetes

TRL particle clearance is impaired in patients with type 2 diabetes [25], contributing to the hypertriglyceridemia of this condition. Postprandial accumulation of chylomicrons and chylomicron remnants is also determined to a large extent by the clearance capacity [26,27]. Aside from impaired clearance, production of apoB-containing lipoprotein particles is increased in type 2 diabetes and insulin resistant states such as the metabolic syndrome. This includes the overproduction of both VLDL [28,29] and chylomicron [14] particles. Specifically, the overproduction of apoB100-containing VLDL particles by the liver and apoB48-containing chylomicrons by the intestine accentuates the accumulation of atherogenic lipoprotein particles in the circulation [30,31]. We have previously demonstrated in humans that: (1) insulin acutely inhibits both VLDL and chylomicron secretion, partly by its suppression of circulating FFA [32–34], an effect that is blunted in insulin resistance [32] and type 2 diabetes [35,36]; (2) circulating FFA acutely stimulate VLDL and chylomicron secretion [33,37]; (3) acute hyperglucagonemia does not directly affect chylomicron secretion but inhibits hepatic VLDL secretion [38]. These findings have recently been reviewed elsewhere [30,31]. In a series of more recent studies, we have expanded our investigation into the role of several additional factors, namely intestinal hormones (GLP-1, GLP-2 and DPP-4 inhibitors that raise the level of these hormones), the polyphenol resveratrol, and we have revisited the role of carbohydrates. In addition, intestinal cholesterol absorption/excretion and bile acid metabolism have emerged as potential players in regulating chylomicron production. These recent findings regarding the mechanisms of intestinal lipoprotein production will be discussed below. Detailed description of chylomicron TG and apoB synthesis and particle assembly in the enterocytes are not discussed. Readers are encouraged to refer to several related recent reviews [30,39,40].

3. Recent findings in the regulation of intestinal lipoprotein production

3.1. Glucagon-like peptide-1 receptor (GLP-1R) agonists

Incretin-based therapies have been in clinical use for the treatment of type 2 diabetes for a number of years. Incretins, including glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP), are intestinally derived hormones, secreted by the intestinal L and K cells, respectively, in response to meal ingestion. The incretins are rapidly degraded by the enzyme dipeptidyl peptidase-4 (DPP-4). GLP-1, through its receptor (GLP-1R), has a number of effects that regulate glucose homeostasis, including enhancing glucose-stimulated insulin secretion by pancreatic beta-cells, slowing gastric emptying, inhibiting glucose-dependent glucagon secretion and promoting satiety [41]. The primary action of GIP is the stimulation of glucose-dependent insulin secretion. Incretin-based therapies, including DPP-4 resistant GLP-1R agonists (also referred to as GLP-1 mimetics) and DPP-4 inhibitors, both have proven efficacy in improving glycemic control in patients with type 2 diabetes [42,43]. Several differences exist between these classes of agents, in that the injectable GLP-1R agonists reduce food intake (i.e. inducing satiety), promote weight loss and inhibit gastric emptying [44,45], whereas DPP-4 inhibitors are administered orally, do not reduce body weight and have minimal effects on satiety [46].