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Model of intestinal chylomicron over-production and Ezetimibe treatment: Impact on the retention of cholesterol in arterial vessels

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Abstract

The metabolic syndrome (MetS) and conditions of insulin resistance are often characterized by an increase in cardiovascular disease (CVD) risk without a concomitant increase in low-density lipoprotein cholesterol (LDL-C), suggesting that other atherogenic pathways maybe involved. Intestinally derived chylomicron remnants (CM-r) are also thought to contribute to atherogenic dyslipidemia during insulin resistance. Recent animal and human studies suggest that insulin resistance leads to an over-production of intestinal chylomicrons (CM), which can contribute to fasting and post-prandial dyslipidemia during these conditions. We and others have contributed new insights into the mucosal absorption, efflux and secretion of cholesterol and triglyceride (TG) in intestinal CM during conditions of insulin resistance. One of the pertinent discoveries has been that the intestine has the capacity to increase the secretion of CM during conditions of hyper-insulinemia (observed in the JCR:LA-*cp* rat model).

Advances to identify cholesterol-transporter targets have highlighted the contribution of the intestine to whole body cholesterol metabolism. Ezetimibe (EZ) is a novel pharmaceutical compound that reduces intestinal cholesterol absorption. We know that Ezetimibe either alone, or in combination with a HMG-CoA reductase inhibitor (such as Simvastatin [SV]) can decrease both plasma LDL-C and CM-r concentrations. However, the combined effects of these compounds (EZ + SV) on post-prandial dyslipidemia and/or impact on arterial deposition of cholesterol during MetS have not been studied. The focus of this review is to highlight studies using an animal model of MetS and CM over-production (the JCR:LA-*cp* rat), and to summarize the effects of Ezetimibe on intestinal cholesterol flux, CM metabolism and uptake of cholesterol into arterial vessels.

Keywords: Lipid metabolism; Insulin resistance; Metabolic syndrome; apoB48; Ezetimibe; Simvastatin; Cholesterol transport; Lipid absorption; JCR:LA-cp rats

Contents

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1. Increased risk of cardiovascular disease during the metabolic syndrome

The MetS is often characterized by an increase in cardiovascular disease (CVD) risk without a concomitant elevation in plasma low-density lipoprotein cholesterol concentration (LDL-C), suggesting that other pathways are contributing to atherogenic risk [1–3]. Recent studies have indicated that intestinal apolipoprotein-B48 (apo-B48) containing chylomicron remnants (CM-r) (in both fasted and post-prandial states), contribute to atherogenesis and are a significant risk factor for CVD ([4] and see other articles in this issue). The consequence of impaired clearance of small dense, cholesterol-rich CM-r contributing to atherogenesis, is proposed to be due to increased arterial exposure, permeability, retention and subsequent accumulation of these particles within the vessel wall [5,6]. Furthermore, evidence from animal and human studies have shown that insulin resistance (IR) can lead to the over-production of intestinally derived CM-r, which may contribute increased circulating concentrations of CM-r associated with post-prandial dyslipidemia [7]. Clinical studies from our own group also suggest that elevated concentrations of CM-r are prevalent during childhood obesity ([8] and abstract by Pendlebury et al., in this issue) and in type 1 diabetic subjects [9], despite the absence of a classical dyslipidemic profile.

2. Using a combination of pharmaceutical targets to inhibit cholesterol absorption and synthesis

It is well established that the total plasma cholesterol concentration is mediated via the metabolic cross-talk between endogenous (hepatic) synthesis and exogenous (intestinal) dietary and biliary reabsorption pathways. HMG-CoA reductase inhibitors (or statins) are widely used for treatment of hypercholesterolemia due to their plasma cholesterol lowering effects by blocking hepatic cholesterol synthesis. In recent years there has been a significant focus to identify cholesterol-transport (absorption) targets that have highlighted the function of the intestine as a major contributor to systemic cholesterol homeostasis. For example, Ezetimibe is a novel pharmaceutical compound that reduces intestinal cholesterol absorption [10]. Ezetimibe either alone, or in combination with statins can decrease the plasma LDL-C and CM-r concentration in humans [11,12]. However, the combined effects of Ezetimibe and statins on post-prandial dyslipidemia and/or arterial retention of CM-r, specifically under conditions of insulin resistance has remained unclear. These questions have been a focus of our group, and thus the purpose of this review is to summarize recent data in the context of known advances in intestinal cholesterol transport, CM metabolism and atherosclerosis.

3. Over-production of chylomicrons during obesity and insulin resistance in the JCR:LA-cp rat

In our laboratory we have developed an adapted lymphatic cannulation (fistulae) procedure that has enabled us to directly measure intestinal lymphatic lipid (triglyceride and cholesterol), as well as apo-B48 (CM) secretion during the basal (fasted) and post-prandial (fed) state. These methods have been invaluable in our understanding of the dynamic flux of lipids derived from the intestine, particularly during conditions of insulin resistance. Using lymph collected from JCR:LA-*cp* rats (a model of insulin resistance and MetS [13,14]), during basal (fasted state) and post-prandial (fed) conditions, we have consistently observed increased concentration of apo-B48 (or the number of CM particles secreted by the intestine) compared to lean (control) rats [4]. Increased production of CM particles in the post-prandial state has been suggested to be an adaptive response as a result of increased lipid availability within the enterocyte during insulin resistance [15,16]. Indeed, the JCR:LA-*cp* rat has been shown to have hypertrophy of the intestinal mucosal villi and an increase in the number of enterocytes per surface area [15]. It is plausible that the intestinal hypertrophy observed in the JCR:LA-*cp* rat may directly contribute to over-production of CM and increased lipid secretion during hyperphagia and/or obesity leading to increased CVD risk.

It is now also recognized that as insulin resistance progresses, the impact on the intestine, specifically enterocyte lipid metabolism is likely to be complex and multi-factorial. For example, an increase in intestinal and intracellular nutrient substrate availability during MetS may also explain enhanced *de novo* lipidogenesis and/or elevated storage capacity. Elegant mechanistic studies by Adeli et al. using a complementary fructose fed hamster model of CM over-production and insulin resistance, has provided breakthroughs in the understanding of intracellular lipidogenic dysfunction in the enterocyte [17], as well as other relevant studies conducted by Hussain et al. [18] and Zoltowska et