Diet and Cardiovascular Health: Chylomicron Remnants and Their Emerging Roles in Vascular Dysfunction in Atherogenesis

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Abstract
Although it has been known for many years that dietary lipids influence the development of atherosclerosis, in the past this has been attributed to their effects on blood cholesterol levels. Recent work, however, has shown that CMRs (chylomicron remnants), the lipoproteins which carry dietary lipids in the blood, potentially have a direct role in initiating atherogenesis by influencing vascular function. The Diet and Cardiovascular Health: Chylomicron Remnants and Their Emerging Roles in Vascular Dysfunction in Atherosclerosis Meeting focused attention on studies which have shown that CMRs influence vascular function via interactions with cells of the artery wall, including endothelial cells and macrophages, and also highlighted the part played by CMRs in the development of premature atherosclerosis in conditions such as the metabolic syndrome, which are an increasing cause of heart disease in developed countries.

Introduction
Dietary lipids are absorbed by the intestine and secreted into lymph in chylomicrons, large triacylglycerol-rich lipoproteins which pass into the blood via the thoracic duct. Here, they are rapidly lipolysed in extrahepatic capillary beds, removing some of the triacylglycerol and leaving smaller CMRs (chylomicron remnants) which deliver the remaining dietary lipids to the liver [1]. Although it has been known for many years that the type of fat in the diet influences the development of atherosclerosis and related CVD (cardiovascular disease) [2,3], in the past, this was mainly attributed to their effects on the levels of cholesterol in lipoproteins such as LDL (low-density lipoprotein) [4], which is known to play an important role in atherogenesis, as it was thought that CMRs were too large to enter the artery wall and therefore could not influence lesion development directly. More recently, however, the work of Mamo and colleagues has demonstrated comprehensively that this idea was mistaken, and that the remnant particles not only penetrate the artery wall, but also are retained in the subendothelial space [5], and there is now considerable evidence to indicate that CMRs are strongly atherogenic [6–8]. The aim of the Diet and Cardiovascular Health: Chylomicron Remnants and Their Emerging Roles in Vascular Dysfunction in Atherosclerosis Meeting was...
to highlight recent studies which have shown that CMRs influence vascular function by interacting with cells of the artery wall, including endothelial cells and macrophages, and which have begun to elucidate the molecular mechanisms involved, and also to discuss the role of the delayed clearance of CMRs in the development of premature atherosclerosis in conditions such as the metabolic syndrome, where postprandial lipaemia is a significant factor in the increased risk of CVD.

CMRs, CVD and Alzheimer’s disease

Although one important way in which dietary fats influence CVD risk is by modulating blood LDL levels [4], a number of studies have indicated that they also have the potential to initiate atherosclerotic lesion development directly during their transport from the gut to the liver in CMRs (for reviews, see [6–8]). Delay in the clearance of CMRs from the circulation has been found to correlate with the development of atherosclerotic lesions [9,10], apoE (apolipoprotein E)-knockout mice, which accumulate remnants in the plasma, develop severe atherosclerosis [11], and remnant-like lipoproteins have been isolated from atherosclerotic plaque [12].

New evidence demonstrating the direct involvement of CMRs in atherogenesis was presented at the meeting by John Mamo, Allen Cooper and Tom Sanders. The adhesion of monocytes to the endothelium is an important initiating event in atherogenesis [13], and Allen Cooper and co-workers highlighted their work showing that human CMRs induce this process, and that this effect is enhanced in conditions where remnant removal from the circulation is delayed. Tom Sanders discussed his studies which have established that postprandial lipaemia causes the activation of clotting Factor VII and impaired endothelium-dependent vasorelaxation.

John Mamo’s talk not only linked CMRs with CVD, but also presented the novel idea that the particles may also be implicated in Alzheimer’s disease. The two conditions have a number of common features in that the risk of developing both is increased by dietary saturated fat and cholesterol, and both involve the deposition of complexes in extracellular matrices followed by an inflammatory response. John presented evidence to suggest that the cerebral deposition of Aβ (amyloid β-peptide), a prominent feature of Alzheimer’s disease, may be related to the metabolism of chylomicrons, and hypothesized that subjects with CVD and/or Alzheimer’s disease may have elevated plasma levels of chylomicrons and CMRs and greater rates of endothelial transport, including across the blood–brain barrier.

CMRs and endothelial dysfunction

Endothelial dysfunction occurs when endothelium-dependent vasodilatation is impaired, and is an early event in atherosclerosis which can be demonstrated before the appearance of visible lesions in the artery wall, a condition in which endothelial cells are activated in a pro-inflammatory and pro-coagulant manner [14]. There is evidence from studies in vivo and in vitro to suggest that remnant lipoproteins cause endothelial dysfunction [6,15–17]. Manuel Castro Cabanas spoke about work from his group showing that, in human subjects, postprandial lipoproteins activate leucocytes and the complement system and up-regulate adhesion molecules on the endothelium, causing endothelial dysfunction and aiding the entry of inflammatory cells into the artery wall ([18], see pp. 466–469). Caroline Wheeler-Jones discussed recent studies using CRLPs (CMR-like particles) and HUVECs (human umbilical vein endothelial cells) which have begun to elucidate the molecular mechanisms involved. CRLPs were found to have pro-inflammatory effects on the cells and to alter the balance of release of vasodilator against vasoconstrictor eicosanoids, effects that may involve NF-κB (nuclear factor κB) and/or MAPK (mitogen-activated protein kinase) signalling pathways ([19], see pp. 442–445). As well as macronutrients such as fatty acids, CMRs carry lipophilic micronutrients such as vitamins and antioxidants. Recent evidence that these minor components can influence the effects of CMRs on endothelial dysfunction, and thus may be beneficial therapeutically, was presented by Javier Perona ([20], see pp. 446–450).

CMRs and macrophage foam cell formation

Fatty streaks, the first visible lesion in atherosclerosis, consist mainly of lipid-engorged macrophage foam cells. Extensive studies have established that LDL has a major role in macropage foam cell formation, but oxidation of the particles, which may occur within the artery wall, is necessary before lipid accumulation is induced [21]. In marked contrast, CMRs do not require prior oxidation to cause extensive lipid accumulation in macropages [6]. Talks by Kathleen Botham ([22], see pp. 454–458) and Elena Bravo ([23], see pp. 459–463) highlighted recent advances in the understanding of the mechanisms involved in the uptake of CMRs by macrophages using CRLPs and macrophages derived from the human monocyte cell line THP-1 or primary human macrophages. It is clear that the apoE-dependent LDL receptor and LDL receptor-related protein play important roles, but extracellular lipolysis appears to be involved in the uptake of fatty acids and the increased triacylglycerol content of the cells, while the selective uptake of cholesteryl esters contributes to cholesterol accumulation. One of the most striking observations is that, contrary to expectations, oxidation of CRLPs is inversely related to their uptake and induction of lipid accumulation by the cells, so that oxidized particle were taken up more slowly, while those protected from oxidation by the incorporation of antioxidants were taken up more rapidly. This surprising finding may provide part of the explanation for the failure of large-scale clinical trials to show any protection against heart disease by dietary supplementation with lipophilic antioxidants such as β-carotene [24].

CMRs and the metabolic syndrome

The metabolic syndrome is an increasingly common condition in Western countries characterized by a number of cardiovascular risk factors, including insulin resistance, obesity,
hypertension and dyslipidaemia [25]. Hypertriglyceridaemia results from overproduction of VLDL (very-low-density lipoprotein) which is combined with impaired chylomicron metabolism, since the two lipoproteins compete for lipolysis by LPL (lipoprotein lipase), and this in turn leads to accumulation of CMRs in the blood. Using fatty acids labelled with stable isotopes given in a test meal (chylomicrons) or intravenously (VLDL) to human subjects, Fredrik Karpe and colleagues [26], see pp. 472–476 have studied the tissue-specific metabolism of the two lipoproteins in adipose tissue and skeletal muscle simultaneously by taking blood samples from the superficial epigastric vein (adipose tissue) and the deep forearm antecubital vein (skeletal muscle), and have found that chylomicrons are a much preferred substrate for LPL in both tissues. In another set of experiments using an immunoaffinity method to isolate remnant lipoproteins, however, adipose tissue was demonstrated to be more efficient in the conversion of chylomicrons into remnants than skeletal muscle. Spencer Proctor’s group have developed the obese JCR-LA corpotulent rat as a model for the metabolic syndrome [27], see pp. 477–481. Plasma fasting and post-prandial apoB48 (apolipoprotein B48), the production of lymphatic chylomicrons and apoB48 particle size were all significantly increased in these rats as compared with lean controls. Using this model, Spencer and his co-workers have developed the hypothesis that the arterial remodelling that accompanies insulin resistance may explain the accelerated trapping of apoB48-containing particles in the artery wall. The development of these new methods will facilitate further studies of the disturbances in lipoprotein metabolism which underlie the development of disorders such as the metabolic syndrome and Type 2 diabetes.

Future directions

The atherogenicity of CMRs is now established, and this meeting has focused attention on the interactions between the particles and cells involved in the events which initiate atherosclerotic lesions, including vascular endothelial cells, leucocytes and macrophages. Many such interactions have been identified and, although some studies have begun to address the mechanisms by which they are mediated, a great deal remains to be done. Understanding the role of CMRs in promoting inflammatory responses and the part played by reactive oxygen species is one of the important challenges for the future. Evidence presented at the meeting also indicates that the interaction of CMRs with the vasculature may be modulated by dietary factors, including different types of dietary fat and minor dietary lipophilic components such as vitamins and plant carotenoids, and we need to discover more about these effects to help in the control of CVD risk by changing the diet rather than by pharmaceutical intervention. In addition, the meeting has highlighted a potential new link between CMRs and Alzheimer’s disease, and this will surely be of great interest for future studies. Finally, the rapidly increasing incidence of obesity, diabetes and the metabolic syndrome in developed countries means that a better understanding of the part played by CMRs in these conditions is a high priority.

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References

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