Lipolysis Needed for Chylomicron Uptake?

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Abstract—Despite clinical evidence that postprandial lipemia and chylomicrons could contribute to atherosclerosis, direct evidence is lacking. The study by Weinstein et al1 provides evidence to suggest that intact chylomicrons might be atherogenic by using genetically altered mice lacking Gpihbp1 protein, which may play a major role in the lipolysis of triglyceride-rich lipoproteins. However, the study does not rule out a contribution by remnants or limited lipolysis by other potential enzymes or pathways. It might be intriguing to determine the contribution of cholesterol derivatives in the chylomicrons to the lesions and the nature of the lesions. (Arterioscler Thromb Vasc Biol. 2010;30:5-6.)

Key Words: atherosclerosis • Gpihbp1 null mice • hypertriglyceridemia

The question of whether plasma triglyceride-rich lipoproteins and their lipolytic products contribute to atherosclerosis has been asked repeatedly for a long time. The slow and negligible arterial clearance of large lipoproteins such as chylomicrons suggest that these lipoproteins themselves are not primarily responsible for arterial lesions. In contrast, a strong correlation between plasma triglycerides (TG), which are predominantly carried in large lipoproteins, and coronary artery disease suggest that there might be other mechanisms by which plasma TG might contribute to the disease. However, as more and more evidence accumulates for the significance of the cholesterol-carrying lipoproteins (low-density lipoprotein and high-density protein) in atherosclerosis, correction for the presence of these lipoproteins diminished the significance of TG-carrying lipoproteins. In lieu of the findings that hypertriglyceridemic subjects often have low high-density protein, it became apparent that TG could be a predictor in the presence of low high-density protein or low-density lipoprotein/high-density lipoprotein ratios. One important missing component in many of the earlier studies is the lack of identification of the origin of the TG between the B48 and B100 lipoproteins. Later studies established a definite link between postprandial lipemia and an association between plasma TG levels and cardiovascular disease. These studies are elegantly described in a review by Zilversmit.2

The correlation of these studies was supported by a solid mechanistic explanation when it was realized that the endothelium-bound TG-rich particles were acted on by lipoprotein lipase, resulting in the depletion of TG and smaller particles. These particles were suggested to “hetero-exchange” cholesterol, thus forming smaller cholesterol-rich particles capable of being atherogenic. Current evidence suggests that macrophages, which are major lipid carriers in the atherosclerotic artery, have receptors for TG-rich lipoproteins, and such lipoproteins carrying apolipoprotein B48 have been observed in the atherosclerotic artery. The mechanisms, however, are still sketchy. Whether they could directly interact with macrophages or whether there is a need for previous modifications (as is expected in the case of low-density lipoprotein) and a need for lipolysis are subject to speculation.

The presence of atherosclerosis in subjects with lipoprotein lipase deficiency prompted Weinstein et al1 to question the need for the lipolytic action using an experimental approach that involved mutant mice lacking a critical protein that is necessary for lipoprotein lipase action. Glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein-1 (GPIHBP1) has been suggested to play a major role in the lipolysis of triglyceride-rich lipoproteins. GPIHBP1 is expressed on the luminal side of the endothelium, binds circulating lipoprotein lipase and chylomicrons, and promotes lipolysis. It appears that GPIHBP1 is required for the processing of both apolipoprotein B48-containing and apolipoprotein B100-containing lipoproteins. Weinstein et al report that GPIHBP1+/− mice fed a chow diet had severe hypertriglyceridemia develop, and nearly all of the lipids were present in large lipoproteins. Cholesterol values were also increased. Of particular interest is that these mice had progressive aortic atherosclerosis develop, although the nature of the foam cell lipids is yet unknown. The studies confirm similar effects observed by others using lipoprotein lipase-deficient animals. Thus, regarding the mechanisms involved, high circulating triglycerides (and increased plasma cholesterol) presumably of dietary origin such as chylomicrons could directly contribute to atherosclerosis without lipoprotein lipase and endothelium-mediated lipolytic events.

Whereas these studies restate that intact TG-rich lipoproteins, even in the absence of lipolysis, could be atherogenic, strict comparison between lipolysis-susceptible and “resis-
tant" animals were lacking. The study by Weinstein et al\(^1\) poses many important questions. Could the smaller increases in plasma cholesterol have played a major role? Could the macrophage foam cells be the result of their poor capacity to release stored TG in the presence of overwhelming levels of TG-rich lipoproteins? Did the foam cell macrophages release their TG content while accumulating only cholesteryl esters? Although the presence of foam cells could be explained by the “intact” TG-rich lipoproteins, how did they influence the chemotactic entry of leukocytes into the subendothelial space? Are there other processes such as oxidative stress arising from the stagnation of large lipoproteins in circulation or enzymes, including phospholipases, which could release free fatty acids to activate the endothelium, resulting in chemotactic recruitment of leukocytes and the increase in the flux of large lipoproteins into the endothelium? The analysis of free fatty acids as well inflammatory and chemotactic markers in these mice should reveal interesting clues of the fundamental mechanisms of atherogenesis. The availability of these mice should shed light on the role of dietary TG and chylomicrons in the development of cardiovascular disease. In addition, the current line of studies would greatly enhance knowledge of the role of factors, such as peroxisome proliferator-activated receptors (PPAR)\(\gamma\), that increase the expression of GPIHBP1.

References


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