Myocardial Ischemia and Lipoprotein Lipase Activity

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It has been >55 years since Hahn first observed that the intravenous injection of heparin abolished postprandial lipemia in dogs; subsequently, Korn and Quigley identified the factor released by intravenous heparin as a triglyceride lipase. Since that time, the putative role of lipoprotein lipase in atherosclerosis has expanded tremendously.

Lipoprotein lipase is a key enzyme in the regulation of lipid fuel disposal, and it provides fatty acids for tissue utilization by catalyzing the hydrolysis of triacylglycerol circulating in triglyceride-rich lipoproteins. Anchored to the surface of the capillary endothelium by glycosaminoglycans, lipoprotein lipase hydrolyzes plasma chylomicrons and VLDL to remnant particles. As such, lipoprotein lipase is the rate-limiting enzyme responsible for the removal of plasma triglyceride-rich lipoproteins from the circulation. Although expressed in most tissues of the body, in particular, skeletal and heart muscle and adipose tissue, lipoprotein lipase is also expressed and secreted by macrophages. Lipoprotein lipase is important for the transfer of phospholipids and apolipoproteins to HDL and, thus, is critical for the formation of this particle. Apolipoprotein C-II is an essential cofactor for the activation of lipoprotein lipase activity, whereas apolipoprotein C-III inhibits activity.

A number of polymorphisms in the lipoprotein lipase gene have been associated with varying degrees of plasma lipoprotein levels and the severity of coronary artery disease. Low levels of lipoprotein lipase activity, as seen with a partial deficiency of lipoprotein lipase, have been associated with the progression of coronary atherosclerosis. Decreased lipoprotein lipase activity and the resultant elevated triglyceride levels and reduced HDL cholesterol levels increase the risk of ischemic heart disease. Low HDL cholesterol levels reduce reverse cholesterol transport. Elevated triglyceride levels indicate that lipoprotein remnants and partially delipidized lipoproteins of differing size and composition, such as VLDL, IDL, chylomicron remnants, and lipoprotein B-containing particles (LP-B:C, LP-B:C:E, and LP-A-II:B:C:D:E), are present in the plasma.

Consistent with these findings are data from 2 large serial coronary angiographic clinical trials indicating that apolipoprotein C-III, a marker of triglyceride-rich lipoprotein metabolism and the clearance of chylomicron and VLDL particles, is an independently significant predictor of the progression of coronary atherosclerosis. These data implicate the inefficient removal of triglyceride-rich lipoproteins by lipoprotein lipase in the progression of atherosclerosis. Decreased removal of chylomicrons and VLDL particles prolongs circulatory residence time and, therefore, increases the exposure of the arterial wall to these atherogenic particles. Low lipoprotein lipase activity may also contribute to atherosclerosis by promoting postprandial lipemia.

In this issue of Circulation, Kastelein et al present further evidence for the relationship between coronary heart disease and lipoprotein lipase activity. The authors demonstrate, in a subgroup of men from the Regression Growth Evaluation Statin Study (REGRESS), a significant relationship between lipoprotein lipase activity and mass and ischemic heart disease, as determined by the severity of angina pectoris according to the New York Heart Association classification for angina pectoris and silent myocardial ischemia on 24-hour ambulatory ECG monitoring. Lipoprotein lipase activity is important in determining both fasting and postprandial triglyceride-rich lipoprotein levels. With a reduced capacity to catabolize triglyceride-rich lipoproteins, there is an increased exposure of the arterial wall to postprandial lipoproteins, which are particularly atherogenic.

Because transient elevations in triglyceride-rich lipoproteins and postprandial lipemia can impair endothelium-dependent vascular function, a possible mechanism for the association of reduced levels of lipoprotein lipase activity and myocardial ischemia involves a reduction in endothelium-dependent vascular reactivity. The symptoms of postprandial ischemia seen in clinical practice are consistent with these findings, but whether endothelial dysfunction causes myocardial ischemia remains to be definitively determined. It would be remiss not to point out, however, that not all studies consistently demonstrate impaired endothelium-dependent vascular function with elevations of triglyceride-rich lipoproteins or low levels of lipoprotein lipase activity. Nevertheless, the report by Kastelein et al is important, because we spend most of our lives in the postprandial state.

Triglyceride-rich lipoproteins clearly play an important role in the progression of atherosclerosis. In fact, both lipoprotein lipase activity and apolipoprotein C-III are independently associated with the progression of mild to moderate lesions (<50% diameter stenosis), the very lesions that predict clinical coronary events. Although lipoprotein lipase may play an important role in atherosclerosis, this role is not straightforward. On the one hand, because efficient lipolysis of triglyceride-rich lipoproteins results in a non-

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atherogenic lipoprotein profile, whereas on the other hand, increased expression of lipoprotein lipase by arterial wall macrophages may be proatherogenic by promoting the retention of LDL particles. In addition, many factors other than the interaction with apolipoproteins affect lipoprotein lipase activity, including insulin sensitivity, insulin levels, body mass, adrenergic stimulation, fatty acid levels, thyroid function, renal function, ethanol use, heparin inhibitors, and a variety of illnesses and disease states. All of these factors either individually or concomitantly modulate the impact of the lipoprotein lipase genotype.

Whether and to what degree lipoprotein lipase is involved in ischemic heart disease remains to be fully elucidated. Untangling the lipoprotein lipase risk for ischemic heart disease from the risk of the lipoproteins that this enzyme regulates may be impossible. However, such a pursuit deserves attention and is justified because of its possible therapeutic implications. As a key regulator of fasting and postprandial lipoprotein catabolism, targeting lipoprotein lipase activity for therapeutic manipulation, such as with thiazolidinedione derivatives, has important implications for the treatment of lipid disorders, the prevention of atherosclerosis and, possibly, myocardial ischemia.

References

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