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Clinical Lipidology Roundtable Discussion

JCL Roundtable: Hypertriglyceridemia due to defects in lipoprotein lipase function

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Abstract: In this Roundtable, our intent is to discuss those rare genetic disorders that impair the function of lipoprotein lipase. These cause severe hypertriglyceridemia that appears in early childhood with Mendelian inheritance and usually with full penetrance in a recessive pattern. Dr Ira Goldberg from New York University School of Medicine and Dr Stephen Young from the University of California, Los Angeles have agreed to answer my questions about this topic. Both have done fundamental work in recent years that has markedly altered our views on lipoprotein lipase function. I am going to start by asking them to give us a brief history of this enzyme system as a clinical entity.


Dr Brown

Dr Brown: In this Roundtable, our intent is to discuss those rare genetic disorders that impair the function of lipoprotein lipase (LPL). These cause severe hypertriglyceridemia that appears in early childhood with Mendelian inheritance and usually with full penetrance in a recessive pattern. Dr Ira Goldberg from New York University School of Medicine and Dr Stephen Young from the University of California, Los Angeles have agreed to answer my questions about this topic. Both have done fundamental work in recent years that has markedly altered our views on LPL function. I am going to start by asking them to give us a brief history of this enzyme system as a clinical entity.

Dr Goldberg: I think people had known for a long time that there was a syndrome of severe hypertriglyceridemia that caused pancreatitis in young children. But the lipase enzyme itself was first uncovered in 1943. Hahn at the University of Rochester was studying methods of measuring red cell volume in dogs. To prevent clotting of his catheters, he injected heparin during the studies. He observed that in dogs that had eaten a fat containing meal and by chance had lipemic plasma, a rapid clearing of the lipemia occurred. Hahn wrote a short paper in *Science* in 1943 describing what he called a lipemia clearing factor that was induced by heparin. This activity was subsequently attributed to an enzyme and renamed LPL. So the discovery of LPL starts in 1943.


Dr Goldberg

The linking of this enzyme to a human disorder was in 1960 when Richard Havel and Robert Gordon made the observation that the children who had severe hyperchylomicronemia and pancreatitis had a defect in LPL action. These investigators obtained postheparin plasma from patients with fasting hyperchylomicronemia and showed that, as opposed to normal, postheparin plasma from these children failed to degrade chylomicrons, ie, hydrolyze the

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chylomicron triglyceride into free fatty acids. Thus, Havel and Gordon connected the human disease that was termed type I hyperlipoproteinemia or familial chylomicronemia syndrome with defective LPL.

Dr Young: Dr Goldberg properly attributes the discovery of postheparin clearing factor to Paul Hahn. He not only showed that the lipemia was cleared by heparin in the dog but that it continued to clear after the plasma was removed from the animal and placed on the laboratory bench. Later, Ed Korn showed that the responsible enzyme, LPL, was present in the heart and that it was released from the surface of blood vessels by heparin. He proposed that LPL cleaved triglycerides into molecules (glycerol and free fatty acids) that were not opalescent (explaining the "clearing" effect of heparin). He also proposed that, in the absence of heparin, LPL-mediated triglyceride hydrolysis occurs in the heart along the surface of blood vessels.


Dr Young

Dr Goldberg: The other piece of the story that is interesting is a couple of years after the Havel paper, others found that postheparin plasma from children who appeared to be LpL deficient was able to hydrolyze triglyceride when it was contained in emulsion particles. This was a surprise and at first seemed to contradict the original observation that hyperchylomicronemia syndrome was due to LPL deficiency. But the key difference in the assays was the use of chylomicrons rather than lipid emulsions, and these seemingly contradictory findings led to the discovery of the second major postheparin lipase enzyme, hepatic triglyceride lipase. Chylomicrons, but not smaller triglyceride-rich emulsions, are a poor substrate for hepatic lipase whose primary in vivo substrates are remnants, intermediate density lipoproteins, and high-density lipoprotein (HDL) phospholipids. We now know that there is a third member of this lipase family in the postheparin plasma, and that is endothelial lipase.

Dr Brown: Well, we now know that the system is involved in removal of triglycerides from lipoproteins produced in the intestine as we absorb fat (chylomicrons) and in the liver as it unloads excess energy delivered from the diet and body stores in the form of very low–density lipoproteins (VLDLs). What are the tissues of origin of the LPL and where is it located in the body?

Dr Young: LPL is synthesized mainly in white and brown adipose tissue and striated muscle (heart and skeletal muscle). However, depending on the sensitivity of the technique used to detect LPL expression, you can find LPL in most tissues. For example, by northern blot or real time - polymerase chain reaction, it is possible to find LPL transcripts in the mouse liver (where LPL is often assumed to be absent). LPL is also expressed at high levels in certain regions of the brain. Why LPL is produced in neurons of the brain remains an enigma, at least as far as I am concerned. Of note, GPIHBP1 is not present in brain capillaries at appreciable levels. For that reason, I strongly suspect that LPL in the brain is not involved in *intravascular* triglyceride hydrolysis and instead plays some other function.

Dr Goldberg: LpL expression appears to be very specific to certain cells. In the brain, the highest level expression is in hippocampal neurons, but LpL messenger RNA is also found in other cortical neurons and Purkinje cells of the cerebellum 4. In the kidney, LpL expression is greatest in the proximal tubules.

For a number of years, there was a hypothesis that fatty acids were a brain satiety signal. Some animal studies in which areas of the brain were exposed to fatty acids seemed to support this idea. However, from the perspective of in vivo physiology, this really made no sense. High blood levels of fatty acids are found during starvation, when you certainly would not wish to curb appetite. Eckel had suggested that triglycerides, that are increased postprandially, rather than free fatty acids were an appetite regulator. He went on to knockout LpL in the hippocampus, and reported that this led to increased weight gain in mice 5.

Dr Brown: So the adult human liver is devoid of LPL?

Dr Young: We rarely work with human liver samples, but LPL transcripts are easily detectable in the mouse liver.

Dr Brown: There is also work independently from that of Dr. Daniel Steinberg's laboratory showing that LPL is made by macrophages in tissue culture, and I believe the data from human arteries is confirmatory.

Dr Young: Yes, indeed, LPL is produced by macrophages.

Dr Goldberg: Macrophages are the only white blood cells that express LpL, and these cells are the major source of LpL within atherosclerotic plaques.

Dr Brown: Since there are macrophages in the liver, this might be one hepatic source of LPL?

Dr Goldberg: Yes. But under some conditions such as fatty liver, LpL expression increases within hepatocytes. It is also synthesized by the vitamin A storing stellate cells.

Dr Brown: There are mysteries in the reasons for certain tissues to contain the lipase but we know that tissues that need or store a source of energy, namely muscle, or that store energy, such as adipose tissue, are the major sources of this enzyme system. However, we also know most of the function is not in the cells of origin. The enzyme must move from the parenchymal cells to the lumenal surface of the capillaries and there set up a complex interface with chylomicrons and VLDL. Dr Young has done groundbreaking studies on this complex transport and activating system for LPL.

Dr Young: There are several important differences in the expression patterns of LPL and GPIHBP1 (the endothelial cell LPL transporter). For most tissues, the pattern of GPIHBP1 expression mirrors that of LPL, with high levels of expression in white adipose tissue, brown adipose tissue, heart, and skeletal muscle. However, there are several noteworthy differences. First, unlike LPL, GPIHBP1 is not expressed at appreciable levels in the brain. The other site where LPL and GPIHBP1 expression differs is the lung. GPIHBP1 is expressed at very high levels in capillaries of the lung, whereas the levels of LPL expression in the