Chylomicronemia Elicits Atherosclerosis in Mice—Brief Report

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Objective—The risk of atherosclerosis in the setting of chylomicronemia has been a topic of debate. In this study, we examined susceptibility to atherosclerosis in Gpihbp1-deficient mice (Gpihbp1−/−), which manifest severe chylomicronemia as a result of defective lipolysis.

Methods and Results—Gpihbp1−/− mice on a chow diet have plasma triglyceride and cholesterol levels of 2812±209 and 319±27 mg/dL, respectively. Even though nearly all of the lipids were contained in large lipoproteins (50 to 135 nm), the mice developed progressive aortic atherosclerosis. In other experiments, we found that both Gpihbp1-deficient “apo-B48-only” mice and Gpihbp1-deficient “apo-B100-only” mice manifest severe chylomicronemia. Thus, Gpihbp1 is required for the processing of both apo-B48- and apo-B100-containing lipoproteins.

Conclusions—Chylomicronemia causes atherosclerosis in mice. Also, we found that GPIHBP1 is required for the lipolytic processing of both apo-B48- and apo-B100-containing lipoproteins. (Arterioscler Thromb Vasc Biol. 2010;30:20-23.)

Key Words: lipoprotein lipase ■ chylomicronemia ■ lipolysis ■ GPIHBP1

Materials and Methods

Gpihbp1−/− mice (>90% C57BL/6) were housed in a barrier facility and fed a 4.5%-fat chow diet. We also bred “apo-B48-only” and “apo-B100-only” Gpihbp1−/− mice (Gpihbp1−/− Apob48/48, Gpihbp1−/− Apob100/100). All experiments were approved by the Animal Research Committee.

Plasma lipid levels were measured with enzymatic kits, and their distribution within lipoproteins was assessed by fast protein liquid chromatography (FPLC). Lipoprotein diameters were measured by laser light scattering. Western blots were performed as described. Sections of the aortic root were stained with Oil Red O, and lesions were quantified as described. Macrophages were stained with a monoclonal antibody against CD68 (Serotec; 1:100).

Results

Gpihbp1−/− mice had lipemic plasma (Figure 1A), and nearly all of the plasma lipids were contained in large lipoproteins (as judged by FPLC; Figure 1B). Also, plasma apo-B48 levels in Gpihbp1−/− mice were increased (Figure 1C and 1D). Gpihbp1−/− mice had triglyceride and cholesterol levels of 2812±209 and 319±27 mg/dL, respectively (n=42; versus 35±5 and 90±6 mg/dL in littermate Gpihbp1+/+ mice, n=24; P<0.0001 for both; Figure 1E).

The fact that amphibians and birds have neither apo-B48 nor GPIHBP1 led Beigneux et al4 to speculate that GPIHBP1 might have arisen in mammals as a new protein specifically...
dedicated to the lipolytic processing of apo-B48–lipoproteins. They further hypothesized that GPIHBP1 might be unimportant for the processing of apo-B100–containing lipoproteins and that mice lacking both apo-B48 and GPIHBP1 might be normolipidemic. Although this hypothesis initially seemed attractive, it was incorrect. *Gpihbp1*−/−*Apob*100/100 mice and littermate *Gpihbp1*−/−*Apob*48/48 mice had very similar plasma lipid levels (Figure 1F). Similarly, *Gpihbp1*−/−
GPIHBP1-deficient mice develop severe chylomicronemia as a result of defective lipolysis of triglyceride-rich lipoproteins. In this study, we address two timely and important issues. First, we show that mice with chylomicronemia develop spontaneous atherosclerosis, despite the fact that most of the lipids in these mice are found in large lipoproteins—lipoproteins that are often considered to be nonatherogenic. Thus, chylomicronemia leads to atherosclerotic lesions, even in mice fed a low-fat chow diet. These findings in mice add plausibility to the concept that chylomicronemia in humans could lead to increased susceptibility to atherosclerosis. Second, we show that the severe chylomicronemia in GPIHBP1−/− mice is not attributable to a selective defect in the processing of apo-B48-containing lipoproteins. Beigneux et al. had hypothesized that GPIHBP1 might be a mammalian protein specifically dedicated to the processing of apo-B48-containing lipoproteins and further speculated that the processing of apo-B100-containing lipoproteins might not depend on GPIHBP1. This speculation is incorrect. The plasma lipid levels and lipoprotein sizes in Gpihbp1−/−/Apob−/− mice are very similar to those in littermate Gpihbp1−/−/Apob100/100 mice (or littermate Gpihbp1−/−/Apob100/48 mice). Thus, GPIHBP1 is required for the processing of both apo-B48-containing lipoproteins and apo-B100-containing lipoproteins.

Finding atherosclerosis in Gpihbp1−/− mice is consistent with a recent report of aortic lesions in Lpl−/− mice that had been rescued with an injection of an LPL adenovirus. The severity of the hypertriglyceridemia in Gpihbp1−/− mice and LPL adenovirus–rescued Lpl−/− mice is quite similar; however, Gpihbp1−/− mice appear to be the most reasonable choice for future research. Gpihbp1−/− mice can be bred in limitless numbers, whereas the production of adenovirus–rescued Lpl−/− mice is more challenging. Also, systemic infections with an adenovirus could cloud the interpretation of mouse atherosclerosis studies.

The lesions in Gpihbp1−/− mice are small and require longer to develop than those of Apoe−/− or Ldlr−/− mice. Nevertheless, these mice will be useful to the research community. With Gpihbp1−/− mice, it should be possible to determine whether the atherogenicity of TRLs depends on their cholesterol content. Also, this model opens the door to defining the impact of different dietary fatty acids (including dietary oxidized fatty acids) on the atherogenicity of TRLs.

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**Disclosures**

None.

**References**


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