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<sup>−/−</sup>), which manifest severe chylomicronemia as a result of defective lipolysis.

Methods and Results—Gpihbp1<sup>−/−</sup> 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

Human and mouse studies have proven that high levels of cholesterol-rich remnants cause atherosclerosis, but the relevance of triglyceride-rich lipoproteins (TRLs) to atherogenesis remains controversial. In part, this controversy stems from the fact that elevated levels of TRLs and remnants often coexist.

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Humans with chylomicronemia have severe hypertriglyceridemia but low levels of cholesterol-rich remnants. Chylomicronemia patients are often assumed to be protected from atherosclerosis because experiments in rabbits had shown that very large lipoproteins cannot enter the arterial wall and were not particularly atherogenic. However, this assumption was recently challenged by the finding of atherosclerotic lesions in 4 chylomicronemia patients with lipoprotein lipase (LPL) deficiency.

Mice lacking Gpihbp1 (Gpihbp1<sup>−/−</sup>) have severe chylomicronemia, even on a low-fat chow diet, as a result of defective lipolysis. Very recently, chylomicronemia has been observed in a young man with a homozygous missense mutation in Gpihbp1. Thus far, no one has examined whether Gpihbp1<sup>−/−</sup> mice have an increased susceptibility to atherosclerotic lesions. In this study, we examined that issue.

We also tackled a second issue; we addressed whether Gpihbp1 is required for the lipolytic processing of both apo-B48–containing lipoproteins and apo-B100–containing lipoproteins.
Figure 1. Lipids and lipoproteins in Gpihbp1<sup>−/−</sup> mice. A, Lipemic plasma in 15-month-old chow-fed Gpihbp1<sup>−/−</sup> mice. B, Distribution of lipids in FPLC-fractionated plasma. C and D, Western blots of Gpihbp1<sup>+/+</sup> (C) and Gpihbp1<sup>−/−</sup> (D) plasma with an apo-B–specific antibody. Apob<sup>100/100</sup> and Apob<sup>48/48</sup> mice were used as controls. E through G, Plasma triglyceride and cholesterol levels in Gpihbp1<sup>−/−</sup>, Gpihbp1<sup>−/−</sup> Apob<sup>48/48</sup> and Gpihbp1<sup>−/−</sup> Apob<sup>100/100</sup> mice on a chow diet. H, Distribution of <em>d</em>&lt;1.006 g/mL lipoprotein diameters in Gpihbp1<sup>−/−</sup> mice on a chow diet (deciles plus the 95% point). The sizes of the <em>d</em>&lt;1.006 g/mL lipoproteins in Gpihbp1<sup>−/−</sup> mice were similar to those observed previously in mouse lymph chylomicrons during active lipid absorption. We did not compare the sizes of lipoproteins in chow-fed Gpihbp1<sup>−/−</sup> mice and diabetic rabbits (such as those studied by Nordestgaard et al). Because the diabetic rabbits examined by Nordestgaard et al were on a high-fat diet, it is possible that their lipoproteins were larger than those in chow-fed Gpihbp1<sup>−/−</sup> mice. I, Median diameters of <em>d</em>&lt;1.006 g/mL lipoproteins in Gpihbp1<sup>−/−</sup> Apob<sup>100/100</sup> and littermate Gpihbp1<sup>−/−</sup> Apob<sup>48/48</sup> mice. J, Median diameters of <em>d</em>&lt;1.006 g/mL lipoproteins in Gpihbp1<sup>−/−</sup> Apob<sup>100/100</sup> mice and littermate Gpihbp1<sup>−/−</sup> Apob<sup>48/48</sup> mice. In the two different experiments shown in panels I and J, the median diameter of lipoproteins in Gpihbp1<sup>−/−</sup> Apob<sup>100/100</sup> mice were different. We do not fully understand the lipoprotein size differences in the two different experiments. The experiments were performed independently, many months apart, on different sets of mice. Both experiments were performed on mice consuming ad libitum diets (not fasting mice), and the mice examined in I were 3 months younger than the mice examined in panel J. In any case, the important point (for the experiments in both I and J) is that lipoprotein sizes in littermates were not affected by Apob genotype.

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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<sup>−/−</sup> Apob<sup>+/+</sup> mice and littermate Gpihbp1<sup>−/−</sup> Apob<sup>48/48</sup> mice had very similar plasma lipid levels (Figure 1F). Similarly, Gpihbp1<sup>−/−</sup>
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−/−ApoB100/100 mice are very similar to those in littermate GPIHBP1−/−ApoB48/48 mice (or littermate GPIHBP1−/−ApoB48/48 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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