On the Mechanisms by Which Human Apolipoprotein A-II Gene Variability Relates to Hypertriglyceridemia

To the Editor:

A recent issue of Circulation contained an interesting study by van’t Hooft et al. reporting a novel functional polymorphism (a T to C substitution at position -265) in the promoter of the apolipoprotein A-II (apoA-II) gene. ApoA-II is the second quantitatively major protein component of HDL. In the above-mentioned study, the -265C allele was associated with decreased plasma apoA-II concentration, enhanced postprandial metabolism of large VLDL, and decreased waist circumference in healthy 50-year-old men.1

Important and rather surprising advances in our understanding of the role of apoA-II have been reported recently and have mainly been produced by analyses of genetically modified mice.2 In line with the findings of van’t Hooft et al.,1 these advances revealed a consistent relationship of apoA-II with non-esterified fatty acids (NEFA) and VLDL triglyceride plasma concentrations. However, whether apoA-II variability causes increased VLDL synthesis, decreased VLDL catabolism, or both remains a matter of controversy.2

We recently studied human apoA-II-transgenic(Tg)-mice2 and control C57BL/6 mice fed a Western high-fat diet (TD 88137, Harlan Teklad) for 32 weeks. As in previous studies,2 fasting cholesterol, triglycerides, and NEFA concentrations were increased in human apoA-II-Tg-mice. We performed oral fat tolerance tests in these mice after oral administration of 100 μL of olive oil. The area under the curve (AUC) of triglyceride concentrations in human apoA-II-Tg-mice was significantly increased compared with that of control mice (18.5±6.1 vs 5.4±1.2; P<0.05). The AUC increase in postprandial triglycerides was due to an increased secretion rate (11.9±8.7 μmol triglycerides · h−1 · Kg−1 in transgenic mice versus 1.5±0.2 μmol triglycerides · h−1 · Kg−1 in control mice; P<0.05) because triglyceride catabolism did not differ (0.85±0.08 pools/h in transgenic mice versus 0.99±0.12 pools/h in control mice). These data contrast with the interpretation of van’t Hooft et al.,1 who suggested that apoA-II polymorphism is associated with enhanced postprandial VLDL clearance. In our opinion, the effect of the human apoA-II polymorphism found in their study could also be reinterpreted as the result, at least in part, of decreased postprandial NEFA levels in plasma of individuals with the -265C allele. In this context, we would like to know whether the authors measured postprandial NEFA and, if so, what the results were. Further, we are curious as to whether they have any other data with regard to this study that rule out the possibility of decreased VLDL synthesis being a mechanism implicated in their findings.

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Response

In our article,1 we reported an association between the -265T/C polymorphism in the promoter of the human apolipoprotein A-II (apoA-II) gene and the postprandial concentration of large VLDL particles. This observation in human subjects is in agreement with several studies in genetically modified mice,2 which demonstrated an impact of apoA-II on triglyceride metabolism, thus underlining the multifunctional roles of apoA-II. There is, however, considerable controversy regarding the mechanism by which apoA-II influences triglyceride metabolism. Unfortunately, the mouse studies reported to date have not resolved the question of whether apoA-II influences synthesis or catabolism (or both) of triglyceride-rich lipoproteins.2 On the basis of the human data, we proposed that the plasma apoA-II concentration influences the ability to remove large VLDL from the circulation during alimentary lipemia, suggesting that apoA-II primarily influences the catabolic pathways of the triglyceride-rich lipoproteins.1 We have thus far found no evidence supporting the hypothesis that apoA-II affects the rate of synthesis of triglyceride-rich lipoproteins. Specifically, no relationship between the -265T/C polymorphism and plasma NEFA levels was observed. Nevertheless, in view of the inherent limitations of our human studies, it is not possible to rule out the possibility of decreased synthesis being a mechanism implicated in our findings. Clearly, it is more appropriate to address this question using genetically modified mice, and the preliminary data reported in the letter from Julve et al may provide an excellent starting point to resolve this issue.

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