Editorial

The Editors invited Dr Henry Ginsberg to review an important topic that is relevant to many kinetic studies of human lipoprotein metabolism, including one in the present issue. Changes in the concentration of a plasma protein are usually thought to involve the balance between its production and clearance, but as Drs Ginsberg and Ramakrishnan point out, in the case of exchangeable apolipoproteins, the change in concentration associated with a particular fraction of plasma lipoproteins may not be from production or clearance. We welcome any editorial correspondence on this issue.

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Kinetic Studies of the Metabolism of Rapidly Exchangeable Apolipoproteins May Leave Investigators and Readers With Exchangeable Results

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In this issue of *ATVB*, Chan et al present interesting results of a study of the effects of atorvastatin and fenofibrate on apolipoprotein CIII (apoCIII) metabolism.[1] Each drug was administered alone, and the study was conducted as a 3-way crossover design with placebo. The authors report that both drugs reduced plasma and very low–density lipoprotein (VLDL) apoCIII. Further, they conclude from their tracer kinetic studies that the fall in VLDL apoCIII levels resulted from increased fractional catabolic rates (FCR) and reduced production rates (PR) of VLDL apoCIII. These results, they note, may provide an insight into the triglyceride-lowering effects of both atorvastatin and fenofibrate, because apoCIII inhibits both lipoprotein lipase activity and removal of remnants via receptor-mediated pathways.

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A close reading of the article raises issues, however, concerning the interpretation and reporting of apolipoprotein production rates when the apolipoprotein being studied is rapidly exchanging between lipoproteins; apoCIII is such an exchangeable apolipoprotein.[2] Early studies with radio-iodinated lipoproteins as a source of apoCIII tracer demonstrated similar fractional removal rates of apoCIII in VLDL and HDL,[3,4] indicative of rapid exchange of apoCIII between those two lipoproteins. Using radio-iodinated lipoproteins, we found evidence that there were both exchangeable and nonexchangeable pools of apoCIII in both VLDL and HDL.[5] We also found very similar FCRs for apoCIII in VLDL and HDL, suggesting, at the least, a common exit from plasma for all apoCIII. Cohn et al presented kinetic data after infusion of deuterated leucine that supported incomplete exchange between VLDL and HDL apoCIII as well as different rates of removal.[6] However, Chan et al[7] very recently provided evidence for complete exchange of apoCIII between VLDL and HDL, ascribing methodological problems as the basis for the observation by Cohn et al.[6] In their article, Chan et al[7] stated: "Although the compartment model [*with separate inputs and outflows in VLDL and HDL*] fits the apoC-III tracer data, the model parameters cannot be estimated with any degree of precision because of the rapid exchange of apoC-III between the VLDL and HDL fractions," Chan and colleagues concluded that they should use a single plasma pool to describe the kinetics of apoCIII in both VLDL and HDL.[1,7]

Leaving aside the issue of whether apoCIII exchanges completely between VLDL and HDL, the conclusion by Chan et al,[7] that they could only model the data as if all the apoCIII in plasma was in a single metabolic pool, raises important issues regarding both the presentation and interpretation of apoCIII tracer data. We, too, believe that a single-pool model for plasma apoC-III kinetics is quite appropriate.[8] However, use of such a model means there is only a single FCR (or FSR) for plasma apoCIII, ie, for VLDL and HDL together. It does not necessarily mean, however, that the individual FCRs

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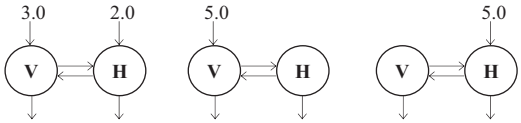

Figure. Three possible models consistent with a plasma apoCIII PR of 5 mg/kg/d: Any VLDL PR and HDL PR that add up to 5 mg/kg/d would fit the tracer data equally well. The removal fluxes, shown without numeric values, are also arbitrary, provided they add up to the plasma PR. V indicates VLDL apoCIII; H, HDL apoCIII. The numbers are apoCIII entry rates in mg/kg/d.

for VLDL and HDL are the same as the overall FCR estimated from the kinetics of the single plasma pool. With the usual definition of FCR as the irreversible outflow divided by the pool mass (and of FSR as the de novo inflow divided by the pool mass), the VLDL apoCIII FCR (and FSR) can have any value between zero and (plasma PR)/(VLDL apoCIII). The same is true for the HDL apoCIII FCR. The rapid equilibration between VLDL and HDL makes it impossible to estimate the individual lipoprotein FCR (or FSR), and even calls into question whether a lipoprotein-specific FCR or FSR for apoCIII is a meaningful concept. Of course, incomplete equilibration (exchangeability) of apoCIII in VLDL and HDL would result in discernible differences in disappearance curves, but that does not appear to be the case here. Once the authors conclude that they could not discern unique FCRs for VLDL and HDL,[7] they are limited, we believe, to estimating a single FCR, and a single PR for plasma apoCIII.

Chan et al[1] have multiplied the plasma FCR by the VLDL apoCIII mass to obtain a VLDL apoCIII PR. But one can imagine many combinations of "true" rates of entry of apoCIII into VLDL and HDL adding up to the calculated plasma PR, any of which would be consistent with the kinetic data. In the Figure, all three models, with very different VLDL and HDL PRs and FCRs, would be consistent with the same enrichment data. Therefore, the plasma FCR and PR are the only interpretable parameters.

Where does that leave the authors in terms of interpreting their results? In the present study by Chan et al,[1] total apoCIII entry into plasma was unchanged whereas fractional removal of apoCIII from plasma was increased; these changes in plasma kinetics were associated with reductions in VLDL apoCIII levels but no change in HDL apoCIII levels. Although at first glance, the interpretation of these results, when presented in this fashion, is unclear, we believe that these are the data that must be presented and interpreted. The straightforward interpretation of the present results is that each treatment increased the efficiency with which apoCIII was removed from plasma; possible explanations would include, as the authors suggest, increased lipolysis of VLDL with removal of free apoCIII from the plasma, increased fractional clearance of apoCIII-containing VLDL (or IDL) remants from plasma, or increased fractional removal of HDL apoCIII from plasma. How each treatment could result in each possible outcome is a matter for speculation (as the authors have done for their conclusion that entry into VLDL is specifically reduced). Further studies, using alternative approaches, will be needed to move from speculated to more detailed insights.

A recent study of apoCIII metabolism that was published in the September issue of *Arterioclerosis, Thrombosis, and Vascular Biology,*[9] appears to raise identical issues as the work by Chan et al.[1] In that study, Pavlic et al concluded that increasing fatty acid flux to the liver via infusion of Intralipid/Heparin resulted in increased secretion of apoCIII into triglyceride-rich lipoproteins (TRL). However, unless those authors observed significantly different rates of fractional clearance of apoCIII in TRL and HDL (they did not provide HDL turnover data), they should have limited themselves to reporting total plasma apoCIII FCR and total apoCIII secretion (production) into plasma.

Disclosures

None.

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