METABOLISM OF APOLIPOPROTEINS AND THE METABOLIC HETEROGENEITY OF APO B IN THE RAT

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The metabolism of the apolipoproteins covers a very broad subject area. I would like to discuss it, in the main, from the somewhat narrower focus of VLDL catabolism in the rat. I would like to point out that it may be rather artificial to consider apolipoprotein metabolism apart from lipoprotein metabolism, but it is becoming increasingly apparent that apolipoproteins may also have a life of their own. In the beginning, of course, there is DNA and messenger RNA which code for the primary sequence of the apolipoproteins and, after signal peptide cleavage, these traverse the cisternae of the endoplasmic reticulum, ending up in the Golgi where much of the final assembly of VLDL takes place, as seen by electron microscopic studies. The liver is the main organ of lipoprotein synthesis, and probably also of catabolism, and it can synthesize all of the known major apolipoproteins: A-I, A-II, A-IV, B, C-I, C-II, C-III, and E. The small intestinal mucosal cells secrete far less apolipoproteins, but the work of Wu and Windmueller has shown that about half of the plasma A-I, and about two-thirds of apo A-IV, are derived from the intestine, which secretes VLDL and HDL as well as chylomicrons. There have been some recent exciting developments bearing on the question of the synthesis of different apolipoprotein isoforms, such as those of apo A-I, and on the involvement of tissues other than liver and intestine which I will only mention briefly. Blue, Williams and co-workers have found that rooster kidney can synthesize apo B and that human kidney and adrenals can make apo E. Schackelford and Lebherz have shown that chick heart muscle can secrete apo A-I; Basu, Brown and Goldstein have found that macrophages from cholesterol-fed mice can synthesize apo E. In this study, they were able to dissociate cholesterol secretion from apo E secretion so that the secretion of an apolipoprotein in association with phospholipid occurred. The point is that not all synthesis and secretion of apolipoproteins
is tied to the assembly of a complete lipoprotein particle of the kind found in the circulation, as I have pointed out some time ago. Quarfordt et al. and Havel and co-workers have found that chylomicrons and VLDL can bind apo C and apo E when incubated in plasma, and it is probable that all apolipoproteins, with the exception of apo B, can move on and off lipoprotein particles in the circulation. The exposure of lipoproteins to endothelial-bound lipases, and to soluble or complexed plasma LCAT (lecithin-cholesterol acyl transferase) and to lipid transfer proteins, makes it difficult to sort out the complex apolipoprotein associations during lipoprotein catabolism.

Apo B metabolism, in particular, has received a great deal of attention, for several reasons, the most important being that it is virtually the only apoprotein of LDL, presumed to be the atherogenic culprit. In 1978, Godfrey Getz and co-workers, briefly reported that the apo B of intestinal chylomicrons had a faster mobility on SDS gels and this was the first clue, in the rat, that there was a difference between apo B secreted by the liver, and that secreted by the intestine. Hepatic VLDL is converted to LDL in the circulation. In rats and mice, the liver secretes both forms of apo B, whereas in all other mammals so far studied, including man, only the higher molecular weight form of apo B is made by the liver. For the sake of simplicity, we shall call this form B_H in contrast to

Fig. 1 Representative SDS-column chromatogram of 3H-amino acid labeled VLDL from fasted (left panel) and fed (right panel) liver perfusates.