Guest Lecture

Postprandial lipid metabolism: an overview

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Since the original investigations of Gage & Fish (1924) on the dynamics of large chylomicron particles during postprandial lipaemia, measurements of triacylglycerol-rich lipoproteins (TRL) after ingestion of fat-rich meals have been utilized to provide information about the metabolism of these intestinal lipoprotein particles *in vivo*. There are many similarities, however, between the metabolism of chylomicrons and hepatogenous VLDL (Havel, 1989), so that observations in the postprandial state may provide generally applicable information about the regulation of TRL metabolism. Recently, it has become possible to distinguish the dynamics of chylomicron and VLDL particles separately by analysing the fluctuations of the concentrations of the two forms of apolipoprotein (apo) B with which they are associated: B-48 and B-100 respectively (Havel, 1994).

The overall pathway of absorption of dietary lipids has long been known and the rapid clearance and metabolism of chylomicron triacylglycerols was appreciated early in this century. The modern era of research in this area, however, had to await the development of methods to separate and characterize plasma lipoproteins (Gofman *et al.* 1949; Havel *et al.* 1955) and was greatly stimulated by the discovery of lipoprotein lipase (*EC* 3.1.1.34; Korn, 1955) and the demonstration that genetic deficiency of this enzyme dramatically reduces the rate of clearance of dietary fat from the blood (Havel & Gordon, 1960). Related physiological studies showed that chylomicron triacylglycerols are rapidly hydrolysed and that their products, free fatty acids (FFA), are concomitantly released and transported in the blood bound to albumin (Havel & Fredrickson, 1956).

DELINEATION OF THE CHYLOMICRON PATHWAY

Early studies of postprandial lipaemia in normal adults showed that all the major lipids of TRL rise and fall together with triacylglycerols (Havel, 1957). These studies also showed that HDL-lipids are affected by fat ingestion, and that HDL-phospholipid concentrations in particular are substantially increased (Havel, 1957; Havel *et al.* 1973*b*). Subsequent studies in animals showed that the metabolism of the second major core component of chylomicrons, cholesteryl esters, differs dramatically from that of triacylglycerols, and led to a two-step model of chylomicron metabolism. In hepatectomized dogs, clearance from the blood of cholesteryl esters of chylomicrons but not triacylglycerols, was substantially impeded (Nestel *et al.* 1963). Furthermore, the majority of triacylglycerol-fatty acids from chylomicrons were taken up by extrahepatic tissues, whereas component cholesteryl esters were removed almost quantitatively by the liver (Bergman *et al.* 1971). The liver also took up 10–20 % of intact chylomicron triacylglycerols in dogs and sheep as well as about one-fifth of the chylomicron triacylglycerol-fatty acids released in extrahepatic tissues by the action of lipoprotein lipase on chylomicron triacylglycerols (Bergman *et al.* 1971). These and other studies in several mammalian species (Redgrave, 1970; Mjøs *et al.* 1975) clearly showed that chylomicrons and also hepatogenous VLDL

are metabolized in two major steps. The first step involves the hydrolysis of chylomicron triacylglycerols and some choline phosphatides by lipoprotein lipase acting chiefly in adipose tissue and striated muscles. Together with transfer of some phospholipids to HDL, this leads to the formation of chylomicron and VLDL remnants. In the second step, chylomicron remnant particles are almost entirely taken up into hepatic parenchymal cells by receptor-dependent endocytosis (Jones et al. 1984; Jäckle et al. 1991). Some VLDL remnants are metabolized similarly, whereas others are further degraded to form LDL.

These developments were followed (or in some cases accompanied) by investigations of the protein components of chylomicrons and their metabolism. Initially these studies showed that most of the chylomicron apolipoproteins of rats, including apo A-I and apo A-IV which are secreted with nascent chylomicrons from the intestine, as well as the C apolipoproteins acquired from HDL after secretion (Imaizumi et al. 1978), are largely transferred to HDL during the first step of metabolism (Havel et al. 1973b; Vigne & Havel, 1981). Apo E, later found to be required for interaction of chylomicron remnants with hepatic receptors, was also shown to transfer to chylomicrons from HDL (Imaizumi et al. 1978; Vigne & Havel, 1981), but remained with the particle as remnants were formed (Mjøs et al. 1975). Then, with the discovery that apo B of chylomicrons is distinct from that of VLDL produced by the liver (Kane et al. 1980), the stage was set for more discrete analysis of postprandial TRL dynamics. In addition, further investigations of the first and second steps of chylomicron metabolism, primarily in experimental animals, clarified the mechanism of action of lipoprotein lipase, including the particular role of apo C-II as a cofactor (Havel et al. 1973a; Connelly et al. 1996), the inhibitory action of all C apolipoproteins on hepatic uptake of TRL (Havel, 1989) and of apo C-I and apo C-III on apo C-II's cofactor property (Havel et al. 1973a), and the regulation of lipoprotein lipase activity and endothelial association by product fatty acids (Peterson et al. 1990). Recent research has also shown that the clearance of chylomicron remnants from the blood involves multiple components on the surface of parenchymal liver cells, including hepatic lipase (EC 3.1.1.3), and the recognition of apo E on remnant particles by endocytic receptors, primarily the LDL receptor, with other receptors, such as the LDL-receptor-related protein, participating in a backup mode (Havel, 1996).

INTESTINAL AND HEPATIC CONTRIBUTIONS TO POSTPRANDIAL LIPAEMIA AND THEIR REGULATION

A number of studies beginning in the 1970s showed that retinyl palmitate, incorporated into the chylomicron core and then taken up irreversibly by the liver with the remnant particles, can be used as a marker of the postprandial chylomicronaemia (Havel, 1994). This approach has been criticized because, in human subjects, retinyl palmitate is transferred from chylomicrons to other circulating lipoprotein particles, so that this molecule progressively becomes a less-selective marker of chylomicronaemia as time passes after ingestion of a fat-rich meal containing added retinol (Krasinski et al. 1990). The advent of methods to quantify apo B-48 and apo B-100 separately in TRL (Bergeron et al. 1996; Karpe et al. 1996) evidently can circumvent this problem, because the apo B components remain exclusively with the chylomicron and VLDL particles until they are removed from the blood. In rodents, but not human subjects, apo B-48 is secreted together with apo B-100 from the liver (van't Hooft et al. 1982), and there is some evidence that the human intestine synthesizes apo B-100 (Hoeg et al. 1990). Our recent studies, in which we have analysed the content of retinyl palmitate in particles containing apo B-48 and apo

B-100 indicate that only very small amounts of apo B-100 are produced by the intestine of adults postprandially (J. Kovar and R.J. Havel, unpublished results).

We (Schneeman *et al.* 1993; Bergeron & Havel, 1995) and others (Karpe & Hamsten, 1995) are now applying quantitative techniques of apo B-48 and apo B-100 analysis to measure the contribution of chylomicrons and VLDL particles to postprandial lipaemia. These studies have shown that the majority, but not all, of the increment in TRL-triacylglycerols after fat ingestion is contained within chylomicron particles, whereas hepatogenous VLDL contribute substantially to the increment in the concentration of TRL particles postprandially (Schneeman *et al.* 1993; Havel, 1994; Bergeron & Havel, 1995, 1996). The concentrations of apo B-48 and apo B-100 in TRL are closely coupled in the post-absorptive state (Schneeman *et al.* 1993; Karpe & Hamsten, 1995), which presumably reflects the common lipolytic mechanism by which remnants are produced from chylomicrons and VLDL. Several lines of evidence suggest that the increase in concentration of VLDL during postprandial lipaemia results from the greater affinity of the larger chylomicrons for lipoprotein lipase on the surface of capillary endothelial cells, thereby increasing VLDL residence time in the blood (Havel, 1994; Björkegren *et al.* 1996). Thus, the residence time of chylomicron triacylglycerols in the blood is normally about 5 min, whereas that of VLDL-triacylglycerols is several-fold longer, even at low VLDL concentrations. As VLDL-particle concentrations increase, however, these particles can compete to a greater extent for lipoprotein lipase. This phenomenon undoubtedly contributes to the strong dependence of the magnitude and duration of postprandial lipaemia on basal plasma and VLDL-triacylglycerol concentrations (Bergeron & Havel, 1997). Although the influence of VLDL-triacylglycerol concentration on the postprandial response can be partially taken into account by statistical techniques, this relationship has the potential to confound experiments comparing subjects with varying concentrations of VLDL particles.

We have recently completed two studies in which comparison groups had identical post-absorptive concentrations of VLDL-triacylglycerols. The results differed from those obtained by others with respect to the influences of dietary fat saturation and apo E phenotype on the postprandial response. We found a slightly greater maximal response of apo B-48 to a meal rich in polyunsaturated fat as compared with a meal rich in saturated fat, but the return to baseline values was similar (Bergeron & Havel, 1995). By contrast, the response of apo B-100 in TRL was prolonged by a habitual diet rich in saturated fat.

In the other study (Bergeron & Havel, 1996), we found prolonged responses of both apo B-48 and apo B-100 to a challenge meal in individuals with apo E_4/apo E_3 phenotype as compared with those with apo E_3/apo E_3 phenotype. It is generally considered that the rate of return to post-absorptive values reflects clearance mechanisms rather than the rate of fat absorption and these results were interpreted to suggest that clearance of remnants of intestinal and chylomicrons and hepatic VLDL is impaired in the presence of an allele specifying apo E_4. This observation raises the possibility that the increased concentration of LDL found among individuals with one or two alleles for apo E_4 may result from increased conversion of VLDL to LDL rather than from impaired LDL catabolism.

Rates of fat absorption are comparable after meals containing equivalent amounts of macronutrients, but these rates are load-dependent, presumably owing to effects of large fat loads on gastric emptying. In this regard, observations of two peaks of lipaemia after a fat-containing meal could suggest that rates of absorption may be biphasic (Bergeron & Havel, 1997), as observed by Gage & Fish (1924) during stressful episodes. Many years ago, Mendeloff (1954) observed that sham feeding a few hours after ingestion of fat could produce rapid increases in plasma triacylglycerols. On the basis of animal experiments, he

proposed that the cephalic phase of digestion is accompanied by emptying of lacteals containing recently-secreted chylomicrons. It is of interest that a second peak in the triacylglycerol response has often followed the ingestion of a second meal low in fat 3–4 h after the first meal (Bergeron & Havel, 1997). Recently, this phenomenon has been shown to reflect rapid entry into the blood of chylomicrons containing fat from the first meal (Fielding, B. A. *et al.* 1995), consistent with Mendeloff's (1954) proposal. Rates of fat absorption are also known to be influenced by macronutrient composition and apparently by subtle cues related to taste and smell (Bergeron & Havel, 1997). Consequently, variations in the rate of increase in lipaemia, at least during the early hours after fat ingestion may well reflect variations in rates of fat absorption and other aspects of intestinal function.

POSTPRANDIAL ALTERATIONS IN OTHER LIPOPROTEINS AND THEIR SIGNIFICANCE

Perturbations of other lipoproteins during postprandial lipaemia may be of considerable functional significance. For example, the alterations in HDL-phospholipids (Havel, 1957; Havel *et al.* 1973*b*) and apolipoproteins (Havel *et al.* 1973*a, b*; Imaizumi *et al.* 1978; Vigne & Havel, 1981) that were noted earlier may influence rates of cholesterol efflux from various cells into the blood. Most of the cholesteryl esters of human chylomicrons are derived from endogenous sources rather than dietary or biliary cholesterol (Dubois *et al.* 1996). Thus, in species such as man with a mechanism for transfer of non-polar lipids between lipoprotein particles via the action of cholesteryl ester transfer protein, postprandial lipaemia is accompanied by movement of cholesteryl esters from HDL and LDL to chylomicrons and VLDL (Bergeron & Havel, 1997). Unesterified cholesterol also moves to the triacylglycerol-rich particles, whereas some triacylglycerols move in the opposite direction (Bergeron & Havel, 1997). The concentration of plasma cholesteryl esters falls slightly during postprandial lipaemia, indicating that removal of cholesteryl esters from plasma exceeds the rate of formation (Bergeron & Havel, 1997). Cholesteryl ester transfer protein activity rises and falls, concomitant with the overall postprandial lipaemic response (Fielding, C. J. *et al.* 1995), and the cholesteryl esters transferred to chylomicrons (and also to VLDL) are presumably taken up by the liver with remnant TRL. Interestingly, the rate of formation of cholesteryl esters through the activity of lecithin–cholesterol acyltransferase (*EC* 2.3.1.43) increases more gradually (Fielding, C. J. *et al.* 1995), in parallel with the rise in HDL-phospholipid concentrations, which may facilitate the enzyme's action. These changes in plasma cholesterol metabolism are accompanied by an increase in the rate of efflux of cholesterol from cells to a species of pre-beta HDL (Castro & Fielding, 1985), so that the overall process by which cholesterol is transported from peripheral cells to the liver (reverse cholesterol transport) is facilitated. The extent to which postprandial lipaemia accelerates this entire process and how it may be perturbed in pathological states remain challenging fields of investigation.

POSTPRANDIAL FATTY ACID METABOLISM

Early studies of chylomicron metabolism showed that lipoprotein lipase exerts a directive force, whereby fatty acids released from chylomicron triacylglycerols are taken up from the site of endothelial hydrolysis into adjacent cells, particularly in adipose tissues (Havel, 1965). An appreciable proportion of the FFA released by action of lipoprotein lipase, however, is returned directly to the blood (Bergman *et al.* 1971; Frayn *et al.* 1994) and in human subjects, about one-third of these are taken up by the liver (Havel *et al.* 1970). After

a mixed meal, FFA levels generally fall owing to inhibition of hormone-sensitive lipase in adipose tissue and net flow of fatty acids into adipocytes occurs (Frayn *et al.* 1994), mainly as a result of insulin's effects on lipolysis and storage of fatty acids. In states of insulin resistance, this appropriate inhibition of lipolysis is blunted and the liver may then be faced with a surfeit of fatty acids derived both from chylomicrons and adipose triacylglycerols (Havel, 1972) which would be expected to increase secretion of triacylglycerols in VLDL (Havel *et al.* 1970). In states of insulin resistance, moreover, the uptake and re-esterification of fatty acids in adipose tissue are likewise blunted, resulting in a vicious circle whereby triacylglycerols tend to accumulate in blood and liver (Havel, 1972, 1974). The accumulation is then compounded by reduced clearance of chylomicron triacylglycerols owing to greater competition for lipoprotein lipase by VLDL-triacylglycerols (Bergeron & Havel, 1997) as well as reduced lipoprotein lipase activity (Havel, 1972, 1974) and inhibition of the enzyme by accumulating fatty acids (Peterson *et al.* 1990). Under these circumstances, clearance of chylomicron and VLDL remnants may also be compromised owing to increased particle flux and, conceivably, from limitation of availability of apo E transferred to triacylglycerol-rich particles as they enter the blood and as remnants are formed (Imaizumi *et al.* 1978; Vigne & Havel, 1981). Further quantitative studies addressing these phenomena would be useful in view of the likely pathogenic role of remnant particles in atherogenesis (Havel, 1994).

EVALUATION OF TRIACYLGLYCEROL-RICH LIPOPROTEIN REMNANTS

The availability of quantitative methods to measure apo B-48 and apo B-100 in TRL has the potential to be very useful in addressing the intestinal and hepatic contributions to postprandial lipaemia, but we still lack satisfactory means to quantify the stage of metabolism of triacylglycerol-rich particles. These particles are heterogeneous not only in size, but also in the composition and conformation of proteins on the surface. The ability to identify and quantify remnant particles would be particularly important. In recent years, an operational definition has been used, based on observations of the accumulation of particle components, particularly retinyl palmitate in individuals with an apo E_2/apo E_2 phenotype (Weintraub *et al.* 1987), who are known to have impaired catabolism of chylomicron and VLDL remnants (Stalenhoef *et al.* 1986). Thus, large particles containing retinyl palmitate (with Svedberg flotation unit (S_f) rates exceeding 400) have been designated as chylomicrons, and small particles with lower rates of flotation as chylomicron remnants (Weintraub *et al.* 1987). This approach, while attractive, is evidently inadequate inasmuch as chylomicron triacylglycerols are rapidly hydrolysed even during the clearance of substantial loads of dietary fat (i.e. it is difficult normally to saturate the lipolytic system; Berr, 1992). Thus, virtually all particles found in plasma containing apo B-48 of whatever size are probably remnants in the sense that they are at least partially lipolysed. The situation is more complex for VLDL, in which the triacylglycerol moiety is hydrolysed at a much slower rate. In the postprandial state, hydrolysis of VLDL-triacylglycerols is even slower, so that the particles containing apo B-100 may be more 'nascent' than in the post-absorptive state.

One approach to the problem of remnant separation and quantification has been to use a monoclonal antibody that recognizes most TRL and almost all smaller particles containing apo B-100 but no particles containing apo B-48 (Campos *et al.* 1992). By combining this anti B-100 monoclonal antibody with a monoclonal antibody to apo A-I on a matrix of Sepharose, a test has been developed to measure cholesterol and triacylglycerols in an unbound fraction that contains all particles containing apo B-48

and a fraction of TRL containing apo B-100 which is not recognized by the anti apo B-100 antibody (Nakajima *et al.* 1993) and is enriched in apo E relative to C apolipoproteins (Campos *et al.* 1992). TRL in the unbound fraction have been termed 'remnant-like particles'. Although this unbound fraction contains chylomicron remnants, as indicated previously, and may contain a portion of the VLDL remnants, it is unlikely to contain all VLDL remnants. Many VLDL remnants are presumably smaller than those found in the unbound fraction (Campos *et al.* 1992) and such remnants also include particles of greater density, i.e. IDL. Other approaches to the separation of VLDL remnants by virtue of their reduced electrophoretic mobility have been developed (Pagnan *et al.* 1977), but these have not been widely adopted. Better methods that can be applied practically in clinical research are still needed.

CONCLUSION

Much has been learned about postprandial lipid metabolism since Gage & Fish (1924) first applied quantitative methods to assess chylomicronaemia more than 70 years ago, particularly during the last half century of research on the role of plasma and lymph lipoproteins in lipid transport. One of the most important lessons that has emerged from such research on postprandial lipid metabolism is that the metabolism of all lipoprotein classes secreted from the liver as well as the intestine is altered profoundly. These alterations provide a useful window on the regulation of plasma lipid metabolism in the non-steady-state. Future research should address the mechanisms of these alterations and their significance for the regulation of lipoprotein-lipid transport as well as the role of lipoproteins in atherosclerosis.

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