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Hypothesis

DEFENESTRATION OF HEPATIC SINUSOIDS AS A CAUSE OF HYPERLIPOPROTEINAEMIA IN ALCOHOLICS

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Summary The hepatic sinusoidal endothelium separates sinusoidal blood from hepatocytes; changes in the porosity of this endothelium may affect the passage of chylomicrons into hepatocytes and influence lipid metabolism. Chronic exposure to ethanol reduces the porosity of the endothelium; this mechanism may underlie the hyperlipoproteinaemia observed in some people who drink heavily.

THE LIVER SIEVE

A POROUS sinusoidal endothelium with multiple open fenestrae and no basement membrane was found in animal livers by electron microscopy after perfusion-fixation,[1,2] and shown in rats to separate large circulating chylomicrons from smaller chylomicron remnants.[3,4] This porous barrier, or "liver sieve", separates the sinusoidal blood from the space of Disse and the hepatocytes—a strategic position for regulation of chylomicron catabolism and lipoprotein metabolism.[5,6] Ultrastructural evidence for its function as a sieve[3,4] has been supported by animal studies of the perfusion of radiolabelled chylomicrons.[3] The selectivity of the sieve is decreased when the fenestrae are dilated, as in short-term ethanol ingestion,[7] and abolished when the endothelium has been destroyed by excessive perfusion pressure.[8] These changes may allow chylomicrons with an excess of dietary fat to reach the hepatocytes, and thereby affect hepatic steatosis.[7,8] Various animal species have been shown to have open fenestrae lining the sinusoids.[6] Large and small polystyrene spheres are also sieved in sheep: only spheres of less than 50 nm diameter are allowed to enter the space of Disse and to come into contact with hepatocytes.[9] Rabbits and chickens have a sinusoidal endothelium only about half as porous as that of rats.[10,11] This low porosity may accentuate the susceptibility of these species to dietary cholesterol by hindering the passage of cholesterol-rich chylomicron remnants from the blood to the hepatocytes for recognition and removal from circulation.[12]

Nicotine renders the rat susceptible to dietary cholesterol and hypercholesterolaemia by constriction of the endothelial fenestrae, causing a reduction of sinusoidal porosity.[13] Adrenaline and noradrenaline have similar effect—a mechanism by which stress could influence atherogenesis.[14] Pantethine lowers cholesterol levels in the rabbit, and increases hepatic sinusoidal porosity by dilation of the fenestrae.[15] In tissue culture, the fenestrae of sinusoidal endothelial cells have also been shown to be sensitive to drugs which act by altering the cytoskeleton.[16-18] In rats, ethanol at first dilates the fenestrae,[7] but prolonged ingestion diminishes their number.[19] In baboons, chronic ethanol

ingestion also leads to a reduction in the density of sinusoidal fenestrae.[20] Human beings who drink heavily, even those without cirrhosis, have hepatic sinusoids that resemble capillaries, with a defenestration of the endothelium and the appearance of a basement membrane.[21]

NEW FINDINGS IN MAN

We have examined human liver sinusoids by perfusion-fixation of small portions of diagnostic needle biopsy specimens wedged in a tapered capillary tube.[22,23] Several specimens were taken from patients with no history of ethanol abuse, and transmission and scanning electron microscopy showed these patients to have the usual fenestrated endothelium with a structure similar to that found in animals (fig 1). A specimen from a 33-year-old publican, with a 10-year history of heavy alcohol intake, was also examined. On light microscopy, his liver exhibited only slight and patchy steatosis and a moderate increase in perisinusoidal fibrosis, but no cirrhosis. Transmission electron microscopy showed collagen and some basement membrane in the space of Disse, which separated the sinusoidal cells from the microvilli of the hepatocytes (fig 2). Scanning electron microscopy showed the endothelium to have a low density of fenestrae (fig 3). This patient also had a severe type V hyperlipoproteinaemia, with chylomicron and very low density lipoprotein (VLDL) triglycerides of up to 55 mmol/l and cholesterol of 16 mmol/l in the $d < 1{\cdot}006$ kg/l ultracentrifugation fraction. The cholesterol in the high density lipoprotein fraction was also raised (2·2 mmol/l).

BLOOD LIPIDS IN ALCHOLICS

Increased blood lipids are found in alcoholics,[24] approximately 25% of whom have hyperlipidaemia.[25] Some alcoholics have hyperlipoproteinaemia, mostly type IV or V.[26,27] Type V hyperlipoproteinaemia is characterised by an accumulation of chylomicrons and VLDL.[25] The combination of alcohol and dietary fat can lead to hypertriglyceridaemia because of a decrease in the activity of lipoprotein lipase and/or apo C–II, a co-factor for lipoprotein lipase.[28-30] In our patient the levels of both post-heparin lipolytic activity and apo C–II were within normal limits. Mendelson and Mello suggested that the triglyceride response in alcoholics is related to the presence of a pre-existing lipoprotein disorder.[31] Alternatively, ethanol may alter the level of triglyceride-rich lipoproteins by modifying the absorption of ingested lipids, the hepatic production of lipids, or their rate of removal from circulation. Early workers suggested that the hypertriglyceridaemia of excess alcohol intake was mainly due to increased hepatic secretion of lipoproteins, but they also noted raised circulatory chylomicrons.[27] Many reports of alcoholic hypertriglyceridaemia describe chylomicron-like bands,[32] as well as pre-β bands, on electrophoresis.[31,32] One group reported that the excess triglyceride induced by alcohol in the absence of dietary fat was transported as a pre-β-lipoprotein but that, when fat was ingested, alimentary particles accumulated as well. In the pre-β-triglycerides, fatty acids provided by diet were nine times more common than those from de novo hepatic lipogenesis;[28] clearance of triglyceride-rich chylomicrons and VLDL may be slowed by a competition for common disposal mechanisms.[28,33] The presence of a high level of chylomicron-like, intestinally-derived lipoproteins in type V alcoholic hypertriglyceridaemia has also been shown by the

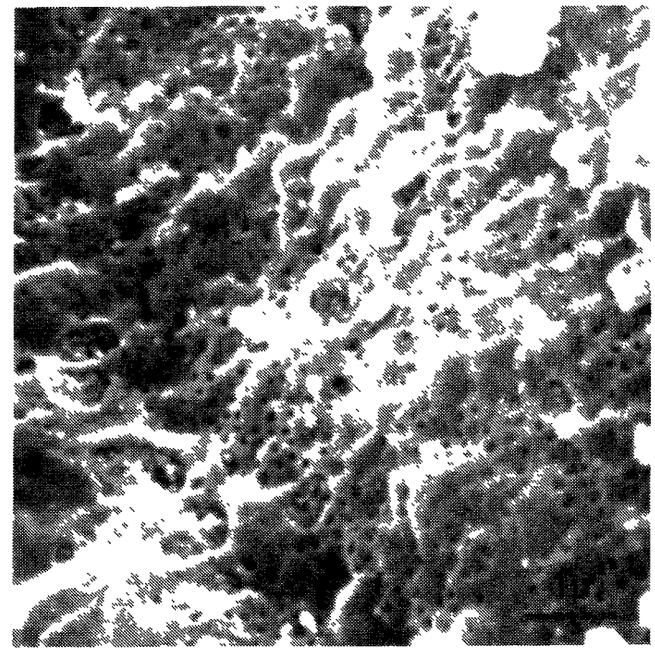

Fig 1—Sinusoidal endothelium of normal human liver tissue.

(× 11 200).

presence of two forms of apolipoprotein B (apo B). Apo B_{48} is synthesised by the intestine and is a marker of chylomicrons, whereas apo B_{100} is derived from the liver:[34,35] apo B_{48} can form up to 10% of the total VLDL fraction in type V hyperlipoproteinaemia.[34] In such individuals, apo B_{48} is removed more slowly from the plasma than is apo B_{100} and patients with type V hyperlipoproteinaemia may therefore have defective catabolism of chylomicron remnants.[35] Schneider et al[36] studied the levels of lipoprotein lipase and hepatic triglyceride lipase and suggested that ethanol-induced hyperlipoproteinaemia results from a combination of increased synthesis and decreased catabolism.

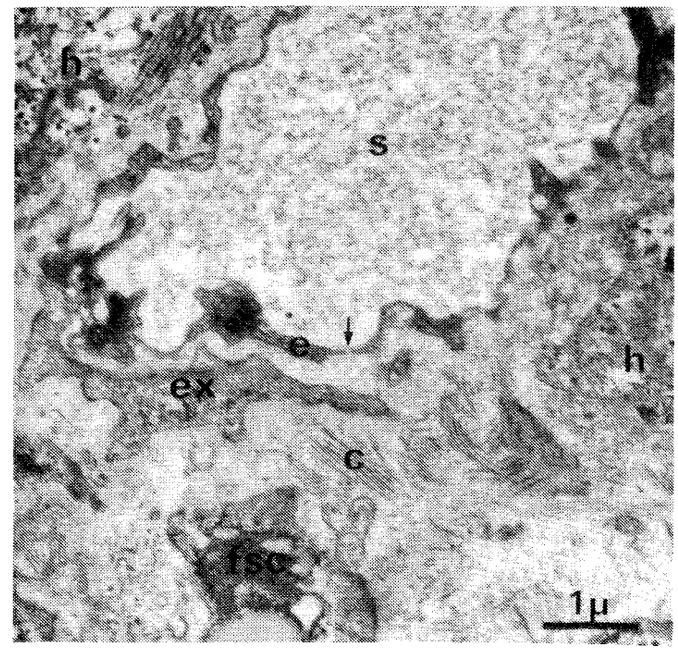

Fig 2—Sinusoid from a patient with alcoholic type V hyperlipoproteinaemia.

Arrow indicates a fenestra; s = sinusoid; e = endothelium, h = hepatocyte; fsc = fat-storing cells; ex = fat-storing cell extension; c = collagen.

(× 11 200).

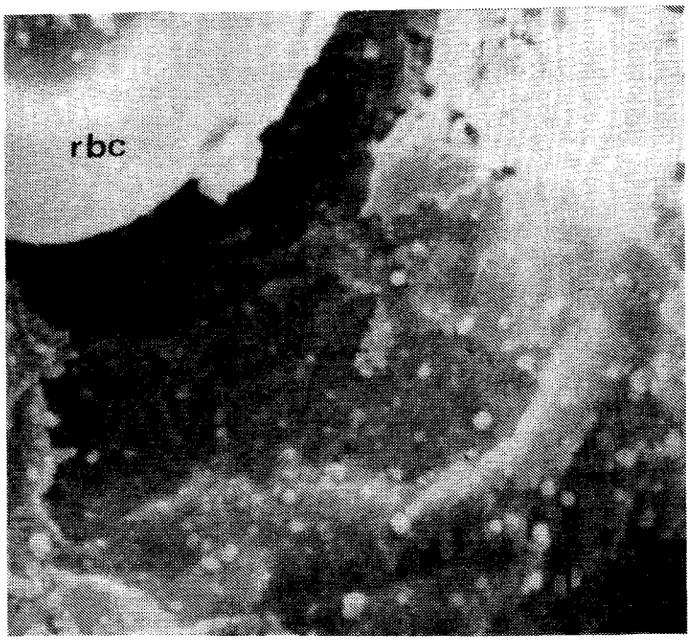

Fig 3—Sinusoidal endothelium of a patient with alcoholic type V hyperlipoproteinaemia.

rbc = red blood cell.
(× 7500).

HYPOTHESIS

We postulate that, in our patient, a decreased porosity of the liver sieve—caused by capillarisation of the sinusoidal endothelium, a reduction in the number of fenestrae, and the presence of collagen within the space of Disse—is a barrier to the usual movement of chylomicron remnants to the hepatocytes for catabolism. This hypothesis would explain the delayed catabolism of apo B_{48}-containing intestinal lipoproteins in alcoholic type V hypertriglyceridaemia. Low porosity of the liver sieve would decrease the passage of chylomicron remnants, while increased liver synthesis of triglyceride-rich lipoproteins would result from a lack of down-regulation of 3-hydroxy-3-methylglutaryl CoA reductase.[6,10] Changes in the porosity of the liver sieve after ethanol ingestion have been reported in animals[7,17,20] and in man.[21] In alcohol-induced type V hyperlipoproteinaemia, abstinence from alcohol substantially reduces the triglyceride levels, which would suggest that the liver sieve regains its normal porosity. We predict that, as in animals, the porosity of the liver sieve in humans will be shown to have a profound influence on lipoprotein metabolism, liver pathology, and atherogenesis.

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