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DANCE ROUND

WE DANCE ROUND *IN A RING AND SUPPOSE,*
'BUT THE SECRET SITS IN THE MIDDLE AND KNOWS.
ROBERT FROST

NEPHROTIC HYPERLIPIDEMIA: IS INHIBITION OF RECEPTOR-MEDIATED ENDOCYTOSIS INVOLVED?

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Hyperlipidemia is a consistent feature of the nephrotic syndrome (NS) and is usually of the Ha or lib Fredrickson type. In cases with severe hypoalbuminemia (15g/l or less) very low density lipoproteins (VLDL) also increase and the ratio of cholesterol to.triglyceride falls (1-4). The nephrotic hyperlipidemia is generally considered to be due to increased hepatic synthesis and secretion of lipoproteins, but there are also investigations showing altered lipoprotein clearance (1,2). Warwick et al. (5) have found a trend towards lower fractional catabolic rate of intermediate density lipoproteins (IDL) and low density lipoproteins (LDL) in nephrotic patients with relatively well maintained serum albumin despite the heavy proteinuria. In another group of nephrotic pateints with lower plasma albumin levels, the amount of LDL cleared by receptor-mediated endocytosis (RME) was only 55% of the value seen in controls, while 60% more LDL were channeled into alternative catabolic pathways (6). In experimental NS, delayed removal of chylomicron remnants was revealed as well (7). Chylomicron remnants are taken up by the liver via the LDL receptor-related protein (LRP). Recently, evidences were provided that receptor for activated <x,-macroglobulin (a_2-macroglobulin-proteinase complex) and the LRP are one and the same entity (8). <x,-macroglobulin seems to control the activity of proteinases not by active site-directed inhibition but by steric shelding and rapid clearance (9). The plasma levels of a_2-macroglobulin are consistently elevated in NS (2), but to the best of my knowledge, there are insufficient data about the uptake of oc_2-macroglobulin-proteinase complexes. Asamietal. (10) reported a glomerular deposition of a_2-macroglobulin in a child with steroid refractory NS, but such depositions were not detected in other nephrotic patients. Biochemical and clinical improvement was observed in this case after treatment with the synthetic proteinase inhibitor camostat mesylate, but the dynamics of a_2-macroglobulin depositions was not examined.

The precise disturbances responsible for the reduced RME of LDL or chylomicron remnants is NS are still unclarified (2). In addition to quantitative, there are also qualitative changes in the lipoproteins of nephrotic subjects (1,2), but Kramer et al (11) have established on cultured human glomerular cells and fibroblasts not reduced binding and internalization of LDL and increased uptake of IDL isolated from nephrotic patients. To the bast of my knowledge, the number of IDL receptors in nephrotic subjects is still not studied. In the investigations reporting not significant differences in the catabolic rate of LDL in NS, the receptor-dependent and the receptor-independent pathways have not been examined separately (1,2).

Capillaries are permeable to water and electrolytes, but relatively impermeable to proteins and the latter

are responsible for the existence of the oncotic pressure gradient across the capillary wall. In NS, hypoalburninemia results both from a loss into the urine and an increase in the fractional catabolic rate. The fall in the plasma oncotic pressure increases the water filtration across the capillaries. This leads to a rise in the lymph flow and the return of fluid from the lymphatic system to the circulation. Because the filtered fluid has low protein content, the concentration of albumin in the interstitial fluid, normally about 50% of that in the serum, falls. By this mechanism, in the nephrotic subjects the oncotic pressure gradient changes little although the considerable decrease in plasma albumin (12,13). Koomans et al (14) have established that when plasma oncotic pressure falls from 23mmHg to 1 OmmHg, the oncotic pressure gradient dropped by only 2-3mmHg (from 10 to 7-8mmHg), i.e., the interstitial oncotic pressure has remained only 2-3mmHg. This results are supported by earlier investigations showing very low protein content of the edema fluid obtained from nephrotic subjects (1-5 g/1) (15) or about 80% reduction of the tissue albumin levels (16). The lymph flow is greatly enhanced in NS and when tissue albumin is almost washed out edema formation takes place (13). Serum sodium concentrations in nephrotic patients appear to be not significantly different from controls (17).

There is no consent about the cause of nephrotic hyperlipidemia and both proteinuria and hypoalbuminemia have been implicated in its pathogenesis (1,2). In NS, hyperlipoproteinemia shows an inverse correlation with serum albumin and there is evidence that thisj correlation reflects changes in the plasma erMfOtic pressure (1,2). Baxter et al (18) and Alien et al (19) have demonstrated that infusions of albumin or other osmotically active substances significantly reduce the plasma levels of cholesterol and triglycerides in nephrotic subjects and that these effects are not due to changes in the lipoprotein lipase activity.

It has been established *in vitro* that hypotonic media inhibits RME by creating unusually flat clathrin lattices (20, and reviewed in 21).
In my option, the data presented above poses two interesting questions: (i) is lowered oncotic pres-

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