LIPOPROTEIN METABOLISM AND ENDOCRINE REGULATION

L. W. Hessel
and H. M. J. Krans
Editors

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LIPOPROTEIN METABOLISM AND ENDOCRINE REGULATION

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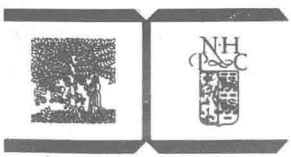
L.W. Hessel *and* **H.M.J. Krans** *Editors*



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PREFACE

Research in the field of human lipid metabolism is strongly motivated by the relationship between blood lipoprotein levels and the pathogenesis of atherosclerosis.

Although it was recognized at an early date that almost all components of the endocrine system can be intimately involved both in atherogenesis and in lipoprotein disorders, most research of the last ten years has been directed at the enzymological and cellular aspects of lipid metabolism and at unravelling the quantitative and qualitative intricacies of the circulating lipoproteins. As a result there has been a rapid development in the analytical accessibility of some major apoproteins, in the recognition of a cellular defect in familial hypercholesterolemia and a renewed interest in the role of the High Density Lipoproteins.

In endocrinology one of the most far-reaching advances is the discovery that hormone action is modulated on the target cell level by changes in receptors and that such changes can sometimes be monitored by binding studies on circulating blood cells. It seems that receptor modulation, already invoked for some time to explain insulin resistance, emerges as a general controlling mechanism. As a result the information gained from the measurement of hormone levels must in many cases be qualified by data on the receptors.

Interaction between these two rapidly growing fields of research has been weak, probably because so many promising approaches are possible within each of these areas. Yet, these same advances are of such a nature that their integration in an overall pattern is necessary for the solution of fundamental questions such as: how are lipoprotein levels in blood regulated and what consequences might be expected for the unsolved problem of atherosclerosis? Thus, when the Committee of Medical Research and Public Health of the Commission of the European Communities recognized the need of an integrated approach to these problems, the opportunity was taken to convene investigators in both fields from major European research centres to discuss lipid metabolism and its hormonal control at a workshop.

In this book the papers presented at his workshop have been collected together with short summaries of the discussions.

There are three parts:

- In section I direct hormonal control (by insulin, corticosteroids, thyroid hormones, etc.) as well as indirect influences (by GIP and other peptides, via the endocrine pancreas) and some pharmacological aspects (e.g. of oral

contraceptives) have been covered.

- Section II is devoted to the modulation of hormonal effects and receptor mechanisms and
- Section III deals with hormonal effects and lipid metabolism in selected organs, especially in the liver.

There is still a long way to go before anything like a satisfactory understanding of the interaction between the regulatory hormones, their receptors, and lipoproteins, their synthesis, secretion, interconversions and catabolism can be expected. Suggestions for a follow-up of this first meeting have been received and plans in this direction might be realized in another one or two years.

The organizers are most grateful to the Committee of Medical Research and Public Health of the European Communities for the help that made this workshop possible.

Leiden, November 1978
L.W. Hessel

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LIPOPROTEIN TRANSPORT AND HORMONE LEVELS

Lipoprotein Metabolism and Endocrine Regulation
L.W. Hessel and H.M.J. Krans editors

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THE METABOLISM OF PLASMA LIPOPROTEINS

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The plasma lipoproteins may be divided into four major classes. Their chemical and physical properties are summarized in Tables 1 and 2.

TABLE 1
CHEMICAL PROPERTIES OF HUMAN PLASMA LIPOPROTEINS

	Protein	Triglyceride (% by weight)	Cholesterol	Phospholipid
Chylomicrons	2.5	85	4	8
VLDL	10	50 - 55	15	18
LDL	20 - 25	12	30	22
HDL	50	6	15	25

TABLE 2
PHYSICAL PROPERTIES OF HUMAN PLASMA LIPOPROTEINS

	Diameter (Å)	Molecular weight	Hydrated density	mobility
Chylomicrons	800	10^9	0,93	origin
VLDL	250-800	10^7	0,97	pre-ß
LDL	175-250	$2,3 \times 10^6$	1,03	ß
HDL_2	85-150	$3,6 \times 10^5$	1,09	$alpha_2$
HDL_3	70- 90	$1,7 \times 10^5$	1,15	$alpha_3$

The protein portion of the lipoproteins consists of multiple heterogeneous proteins known as apolipoproteins. Studies of the regulation of serum lipid concentration require not only consideration of the lipoproteins but also consideration of the apoprotein components of the lipoproteins (Table 3).

TABLE 3
APOLIPOPROTEINS OF HUMAN SERUM

Apolipoprotein	Density class	mol.wt. x 10 $^{-3}$	concentration (mg/dl)
A-I	HDL	28	80 - 120
A-II	HDL	17	30 - 50
A-III	HDL	21	2 - 4
B	LDL, VLDL	275	70 - 90
C-I	VLDL, HDL	7	3 - 7
C-II	VLDL, HDL	8,5	3 - 5
C-III	VLDL, HDL	8,5	8 - 12
E	VLDL, HDL	39	3 - 6
D-2	HDL	7	1 - 2

The best characterization of the apoproteins is the determination of the amino acid composition and of the terminal amino acid. Alternatively, the apolipoproteins can be characterized by their migration rate in defined polyacrylamide gel systems and/or their immunochemical properties. The major function of apolipoproteins is their ability to stabilze lipid micelles during the transport in blood and chyle. Some of the apolipoproteins have been found to have specific physiologic functions. Apoprotein C-II is an activator of lipoprotein lipase, while apoprotein A-I has been shown to be the activator of lecithin-cholesterol acyltransferase. In addition to the functions mentioned above, apolipoproteins play an important role for lipid metabolism in general. As evidenced from the disorders Tangier disease and hyperbetalipoproteinemia, both apoprotein A-I and apoprotein B are of critical importance in maintaining cellular cholesterol balance. In the absence of apoprotein A-I and HDL from plasma (Tangier disease), cholesteryl

esters accumulate in tissue macrophages, Schwann cells, and intestinal smooth muscle cells; the activity of the key enzyme in sterol biosynthesis in man, hydroxy-methylglutaryl-coenzyme A reductase, is regulated by a negative feedback mechanism through apolipoprotein B.

CHYLOMICRONS

Chylomicrons are particles that in normal subjects appear after ingestion of a fatty meal and in certain types of hyperlipoproteinemia. In serum samples they tend to separate in a creamy layer when serum is refigerated overnight. The low density reflects their high triglyceride content. On agarose electrophoresis, they do not move from origin. The major function of the chylomicrons is the transport of dietary or exogenous triglycerides. Chylomicrons are synthesized within the Golgi apparatus of the intestinal mucosa and traverse the lymphatic system to the thoracic duct where they enter the blood stream.

Valuable information concerning chylomicron formation can be obtained from studies of the rare familial disorder, abetalipoproteinemia. Patients with this disorder have fat malabsorption; apoprotein B is completely absent from the plasma and there are no circulating chylomicrons, VLDL, or LDL. This disorder reveals that synthesis of apoproteins and in particular the synthesis of apoprotein B is essential for the formation and/or secretion of triglyceride-rich particles from the liver and the gut.

Chylomicrons are removed from the circulation faster than any of the other lipoprotein classes. The half-life of chylomicron triglycerides in circulation is less than 1 hour in humans. Under physiologic conditions, chylomicron catabolism proceeds in two steps. About 80 % of the triglyceride moiety of chylomicrons is catabolized by muscle and adipose tissue; most of the cholesteryl ester moiety of chylomicrons is catabolized by the liver. The enzyme responsible for triglyceride hydrolysis of the chylomicrons, extrahepatic lipoprotein lipase, is bound to the capillary endothelial cells in muscle and adipose tissue and can be released by