Lipoprotein Metabolism

Edited by
Heiner Greten

Springer-Verlag
Berlin Heidelberg New York

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With 72 Figures

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Symposium on Lipoprotein Metabolism
Held in Heidelberg, Max-Planck-Haus, Berliner Straße 10, Federal Republic of Germany, September 10–13, 1975

This book is edited by
Prof. Dr. HEINER GRETEN, Klinisches Institut für Herzinfarktforschung an der Medizinischen-Universitätsklinik, Bergheimer-Str. 58, D–6900 Heidelberg, Federal Republic of Germany

ISBN 3-540-07635-2 Springer-Verlag Berlin Heidelberg New York
ISBN 0-387-07635-2 Springer-Verlag New York Heidelberg Berlin

Offsetprinting and Binding: Julius Beltz, Hemsbach/Bergstr.

Foreword

An International Symposium on Lipoprotein Metabolism was held in Heidelberg in September 1975. This meeting was planned and organized by Dr. HEINER GRETEN. The field of atherosclerosis research is developing rapidly. Over the past ten years a tremendous amount of new data has been gathered with regard to the composition and structure of lipoproteins and its component lipid and protein moieties. The amino acid sequence of several apoproteins has been elucidated. The physical resolution of the various lipolytic enzymes has opened the way to complete characterization of them, and may eventually help to better understand the underlying defects in lipid disorders. The major cause of death in the Western world is vascular disease and among the different forms it is especially atherosclerotic heart disease. It has become more and more obvious that atherosclerosis is a multifactorial disease and we must take into consideration the many so-called risk factors in planning successful approaches to the prevention of atherosclerotic vascular disease. Without any doubt, one of the foremost risk factors is hyperlipoproteinemia. The participants in this symposium and contributors to this volume include many of the most eminent workers in the world in the field of lipoprotein metabolism and its relationship to atherosclerosis. Probably one of the greatest advantages of this book is that it includes current work which is pertinent to the important topics of the day.

Three years ago a new Institute for Cardiovascular Research was established at the Department of Internal Medicine in Heidelberg. Succesful work of such an institute depends to a great deal on international collaboration and in particular on the exchange of ideas among scientists. I hope that the proceedings of this international symposium will suggest fruitful directions for further clinical investigation in the field of lipid and lipoprotein metabolism. I would like to thank Dr. HEINER GRETEN for both organizing this meeting and editing this book. The rapid publication of the proceedings through Springer Publishing Co. is greatly appreciated.

Heidelberg, February 1976 GOTTHARD SCHETTLER

List of Contributors and Participants

ALLAM, S., Dr. rer. nat., Institut für Arteriosklerosеforschung, 4400 Münster (Westf.), Federal Republic of Germany

ASSMANN, G., Priv.-Doz. Dr. med., Universitätskliniken, Abteilung für klinische Chemie, 5000 Köln, Federal Republic of Germany

AUGUSTIN, J., Dr. med., Klinisches Institut für Herzinfarktforschung an der Medizinischen Universitätsklinik, 6900 Heidelberg, Federal Republic of Germany

AVOGARO, P., Professor Dr., Centro per le Malattie Endocrino Metaboliche, Ospedale Regionale, 30122 Venezia, Italy

BAGINSKY, M., Ph.D., Assistant Research Biochemist, University of California, San Diego, School of Medicine, La Jolla, USA

BALLANTYNE, D., M.D., King Gustaf V Research Institute, Karolinska Hospital, 10401 Stockholm, Sweden

BENGTSSON, G., Dr., Section on Physiological Chemistry, Umeå University, 90187 Umeå, Sweden

BERMAN, M., Ph.D., Acting Chief, Laboratory of Theoretical Biology, National Cancer Institute, National Institutes of Health, Bethesda, USA

BILHEIMER, D.W., M.D., Assistant Professor of Internal Medicine, University of Texas, Health Science Center at Dallas, Dallas, USA

BLUM, C.B., Medical Resident, Department of Medicine, Peter Bent Brigham Hospital, Boston, USA

BOBERG, J., M.D., Associate Professor of Medicine, University of Uppsala, Department of Geriatrics, 75127 Uppsala, Sweden

BOHMFALK, H.A., Research Technician, University of Texas, Health Science Center, Dallas, USA

BROWN, M.S., Associate Professor of Medicine, University of Texas, Health Science Center, Dallas, USA

BROWN, W.V., M.D., Associate Professor of Medicine, University of California, San Diego, School of Medicine, La Jolla, USA

CAREW, T.E., Ph.D., Assistant Research Physiologist, Division of Metabolic Disease, Department of Medicine, University of California, San Diego, La Jolla, USA

CARLSON, L.A., Professor, King Gustaf V Research Institute, Karolinska Hospital, 10401 Stockholm, Sweden

CAZZOLATO, G., M.D., Centro per le Malattie Endocrino Metaboliche, Ospedale Regionale, 30122 Venezia, Italy

CHAJEK, T., M.D., Department of Medicine B & Lipid Research Laboratory, Hadassah University Hospital, Hebrew University, Hadassah Medical School, Jerusalem, Israel

CREPALDI, G., Professor Dr., Istituto di Medicina Clinica dell' Universitá di Padova, 35100 Padova, Italy

EHNHOLM, C., M.D., Department of Serology and Bacteriology, University of Helsinki, 00290 Helsinki, Finland

EISENBERG, Shlomo, M.D., Associate Professor of Medicine, Hadassah Medical Organization, Lipid Research Laboratory, Department of Medicine B, Jerusalem, Israel

FEDDER, W., Dr. rer. nat., Institut für Arteriosklerosеforschung, 4400 Münster (Westf.), Federal Republic of Germany

FELLIN, R., M.D., Istituto di Medicina Clinica dell' Universitá di Padova, 35100 Padova, Italy

FREEZE, H., P.D., Fellow, University of California, San Diego, School of Medicine, La Jolla, USA

GLOMSET, John A., Professor of Medicine, Adjunct Professor of Biochemistry, Department of Medicine and Biochemistry, University of Washington, Seattle, USA

GOLDSTEIN, J.L., Head, Division of Medical Genetics, University of Texas, Health Science Center, Dallas, USA

GOTTO, A.M., Jr., M.D., D. Phil., Professor of Medicine and Biochemistry Scientific Director, National Research

GRETEN, H., Professor Dr. med., Klinisches Institut für Herzinfarktforschung an der Medizinischen Universitätsklinik, 6900 Heidelberg, Federal Republic of Germany

GRIES, F.A., Professor Dr. med., Diabetes-Forschungsinstitut an der Universität Düsseldorf, 4000 Düsseldorf, Federal Republic of Germany

GRUNDY, S.M., M.D., Ph.D., Associate Professor of Medicine, University of California, San Diego, Veterans Administration Hospital, La Jolla, USA

GRUNDERT-REMY, U., Dr. med., Medizinische Universitätsklinik, 6900 Heidelberg, Federal Republic of Germany

HAASE, W., Dr. rer. nat., Dipl.-Kaufm., Institut für numerische Statistik, 5000 Köln-Lövenich, Federal Republic of Germany

HAVEL, R.J., M.D., Director, Cardiovascular Research Institute and Professor of Medicine, University of California, School of Medicine, San Francisco, USA

HELGESON, J., Research Technician, University of Texas, Health Science Center, Dallas, USA

HEUCK, C., Dr. med., Dr. rer. nat., Klinisches Institut für Herzinfarktforschung an der Medizinischen Universitätsklinik, 6900 Heidelberg, Federal Republic of Germany

HÖÖK, M., Dr., Department of Medical Chemistry, Royal Veterinary College, 75123 Uppsala, Sweden

HORSCH, A., Dr. med., Medizinische Universitätsklinik, 6900 Heidelberg, Federal Republic of Germany

JACKSON, R.L., Ph.D., Associate Professor of Experimental Medicine and Cell Biology, The Methodist Hospital, Houston, Texas

KANE, J.P., M.D., Ph.D., Assistant Professor of Medicine, Cardiovascular Research Institute, School of Medicine, University of California, San Francisco, USA

KHOO, J.C., Ph.D., Assistant Research Biochemist, Division of Metabolic Disease, Department of Medicine M-013, University of California, San Diego, La Jolla, USA

KLEMENS, U.H., Dr. med., Klinikum Steglitz der Freien Universität Berlin, 1000 Berlin, Federal Republic of Germany

KLÖR, H.U., Dr. med., Medizinische Universitätsklinik Ulm, 7900 Ulm, Federal Republic of Germany

KLOSE, G., Dr. med., Klinisches Institut für Herzinfarktforschung an der Medizinischen Universitätsklinik, 6900 Heidelberg, Federal Republic of Germany

KOSCHINSKY, T., M.D., Research Fellow, Division of Metabolic Disease, Department of Medicine M-013, University of California, San Diego, La Jolla, USA

LANG, D., Priv.-Doz. Dr. med., Boehringer Mannheim GmbH, Abt. Medizinische Forschung, 6800 Mannheim, Federal Republic of Germany

LEES, Ann M., Research Associate, Arteriosclerosis Center, Massachusetts Institute of Technology, Cambridge, USA

LEES, R.S., Professor of Cardiovascular Disease and Director, Arteriosclerosis Center, Massachusetts Institute of Technology, Cambridge, USA

LEVY, R.J., Director, National Heart and Lung Institute, National Institutes of Health, Bethesda, USA

LINDAHL, U., Professor, Department of Medical Chemistry, Royal Veterinary College, 75123 Uppsala, Sweden

LITHELL, H., M.D., Department of Geriatrics, University of Uppsala, 75127 Uppsala, Sweden

LUSKEY, K., Postdoctoral Fellow, University of Texas, Health Science Center, Dallas, USA

MANGOLD, H.K., Professor Dr. med., Institut für Biochemie und Technologie, H.P. Kaufmann-Institut der Bundesanstalt für Fettforschung, 4400 Münster (Westf.), Federal Republic of Germany

MIDDELHOFF, G., Dr. med., Klinisches Institut für Herzinfarktforschung an der Medizinischen Universitätsklinik, 6900 Heidelberg, Federal Republic of Germany

MÖHRL, H., Professor Dr. med., Medizinische Universitätsklinik, 6900 Heidelberg, Federal Republic of Germany

MOK, H.Y.I., M.D., Assistant Professor of Medicine, University of California, San Diego, Veterans Administration Hospital, San Diego, USA

MORRISETT, J.D., Ph.D., Assistant Professor of Experimental Medicine, The Methodist Hospital, Houston, USA

MYANT, N.B., M.D., MRC Lipid Metabolism Unit, Hammersmith Hospital, London W12 OHS, Great Britain

NOTHHELFER, A., Chemotechniker, Medizinische Universitätsklinik, 6900 Heidelberg, Federal Republic of Germany

ÖSTLUND, A.M., Department of Geriatrics, University of Uppsala, 75127 Uppsala, Sweden

OETTE, K., Professor Dr. med., Abteilung für Klinische Chemie der Universitätsklinik Köln, 5000 Köln, Federal Republic of Germany

OLIVECRONA, T., Professor, Section of Physiological Chemistry, Umeå University, 90187 Umeå, Sweden

OLSSON, A.G., M.D., King Gustaf V Research Institute, Karolinska Hospital, 10401 Stockholm, Sweden

OSTER, P., Dr. med., Klinisches Institut für Herzinfarktforschung an der Medizinischen Universitätsklinik, 6900 Heidelberg, Federal Republic of Germany

PAGNAN, A., M.D., Postdoctoral Research Fellow, Cardiovascular Research Institute, University of California, School of Medicine, San Francisco, USA

POWNALL, H.J., Ph.D., Assistant Professor of Experimental Medicine, The Methodist Hospital, Houston, USA

RAETZER, H., Dr. med., Klinisches Institut für Herzinfarktforschung an der Medizinische Universitätsklinik, 6900 Heidelberg, Federal Republic of Germany

REICHL, D., M.D., MRC Lipid Metabolism Unit, Hammersmith Hospital, London W12 OHS, Great Britain

SAILER, S., Professor Dr. med., Medizinische Universitätsklinik, 6020 Innsbruck, Austria

SAUAR, J., M.D., Rikshospitalet, Medisinsk Avdeling A, Universitetsklinikk, Oslo, Norway

SHAW, W., Ph.D., M.D., Visiting Scientist, University of San Diego, School of Medicine, La Jolla, USA

SCHAEFER, E.J., Staff Associate, Molecular Disease Branch, National Heart and Lung Institute, National Institutes of Health, Bethesda, USA

SCHELLENBERG, B., Dr. med., Klinisches Institut für Herzinfarktforschung an der Medizinischen Universitätsklinik, 6900 Heidelberg, Federal Republic of Germany

SCHETTLER, G., Professor Dr. med. Dr. h.c., Medizinische Universitätsklinik, 6900 Heidelberg, Federal Republic of Germany

SCHLIERF, G., Professor Dr. med., Klinisches Institut für Herzinfarktforschung an der Medizinischen Universitätsklinik, 6900 Heidelberg, Federal Republic of Germany

SEIDEL, D., Professor Dr. med., Medizinische Universitätsklinik, 6900 Heidelberg, Federal Republic of Germany

SPARROW, J.T., Ph.D., Assistant Professor of Experimental Medicine, The Methodist Hospital, Houston, USA

STEIN, O., M.D., Professor of Experimental Medicine, Department of Experimental Medicine and Cancer Research, Hebrew University, Hadassah Medical School, Jerusalem, Israel

STEIN, Y., M.D., Professor of Medicine, Department of Medicine B & Lipid Research Laboratory, Hadassah University Hospital, Hebrew University, Hadassah Medical School, Jerusalem, Israel

STEINBERG, D., M.D., Ph.D., Professor of Medicine and Head, Division of Metabolic Disease, Department of Medicine M-013, University of California, San Diego, La Jolla, USA

STOFFEL, W., Professor Dr. rer. nat., Dr. med., Institut für Physiologische Chemie der Universität, 5000 Köln 41, Federal Republic of Germany

THOMPSON, G., M.D., FRCP, MRC Lipid Metabolism Unit, Hammersmith Hospital, London W12 OHS, Great Britain

TORSVIK, H., M.D., Rikshospitalet, Medisinsk Avdeling A, Universitetsklinikk, Oslo, Norway

VANDERHOEK, J., Ph.D., Lecturer in Biochemistry, Hadassah University Hospital, Hebrew University, Hadassah Medical School, Jerusalem, Israel

WEINSTEIN, D.B., Ph.D., Assistant Research Biochemist, Division of Metabolic Disease, Department of Medicine M-013, University of California, San Diego, La Jolla, USA

WEIZEL, A., Priv.-Doz. Dr. med., Medizinische Universitätsklinik, 6900 Heidelberg, Federal Republic of Germany

Contents

I. Lipolytic Enzymes

Chairmen: H. GRETEN and J. BOBERG

Lipases and Lipoproteins

W. V. BROWN, W. SHAW, M. BAGINSKY, J. BOBERG, and J. AUGUSTIN

The degradation of triglyceride-rich plasma lipoproteins and the uptake of their lipid constituents by tissues is dependent on enzymatic activities which reside on or near the luminal surface of the capillary endothelium. Intravenous heparin injection releases a group of lipid hydrolyzing activities that are not normally present in plasma. As a result, the study of postheparin lipolytic activities (PHLA) has occupied many investigators for more than three decades.

The Activities

A variety of different substrates are hydrolyzed by PHLA. These include triglyceride, diglyceride, monoglyceride, phospholipid, and long-chain fatty acyl coenzyme A. The activities against partial glycerides and phospholipids are of interest because these substrates are also constituents of plasma lipoproteins. Often, however, the conditions for the assays are quite foreign to any that are likely to exist in vivo.

The Enzymes

PHLA contains two major isoenzymes with triglyceride hydrolase activity. By kinetic criteria the first of these is identical to the lipoprotein lipase (LPL) of adipose tissue, muscle, and other extrahepatic tissue. The second is hepatic in origin and differs from LPL in not requiring an apolipoprotein cofactor for full activity (1). In addition, the liver triglyceride lipase (L-TGL) is activated at concentration, the hepatic triglyceride lipase (H-TGL) is activated at concentralipase (2). H-TGL has a lower affinity for heparin as judged by heparin-Sepharose chromatography, and is released into plasma earlier and circulates longer than LPL after large doses of intravenous heparin (Fig. 1).

LPL has been highly purified from milk (3) and from the plasma and adipose tissue of both rat (4, 5) and swine (6, 7). Homogenous preparations of plasma H-TGL were first prepared in the human (8). Only recently have the two enzymes been isolated simultaneously in preparations sufficiently pure to allow parallel comparative studies on their chemical properties. These studies are discussed in a companion paper in this volume.

The diglyceride hydrolase activity in PHLA appears to be completely attributable to the sum of the contribution by H-TGL and LPL. Monoglyceride hydrolase, however, may be due primarily to H-TGL since this enzyme retains significant activity in its purified form (1). With LPL monoglyceride accumulates in the reaction products during hydrolysis of di- and triglycerides (9). Under certain assay conditions little if any hydrolysis of monoglycerides can be demonstrated with

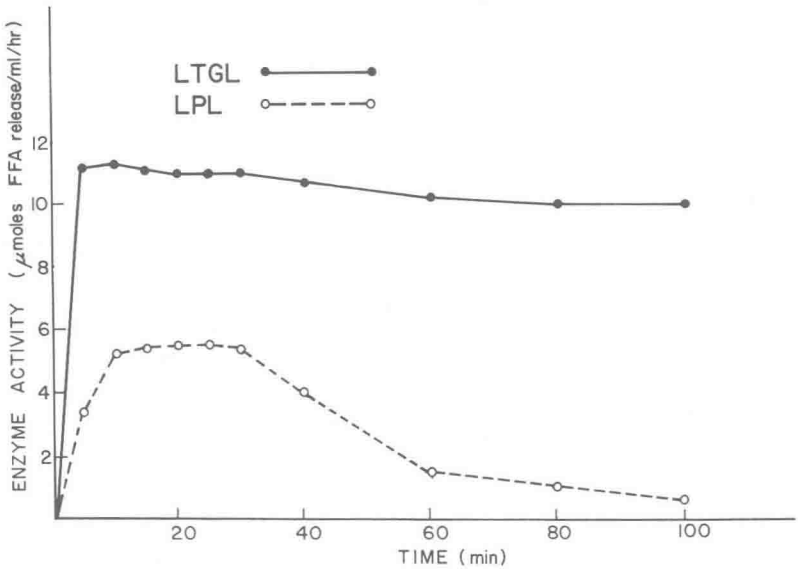

Fig. 1. Human plasma lipolytic activities after i.v. heparin injection (60 U/kg). Triglyceride lipase activity was measured after separation of the hepatic (H-TGL) enzyme from lipoprotein lipase (LPL) on small columns (1 ml) of heparin-Sepharose. LPL was assayed at pH 8.2 in 0.12 M NaCl, 0.2 M Tris-HCl with the apolipoprotein CII (20 μg/ml) as activator. The assay medium for H-TGL was 0.2 M Tris-HCl, 0.75 M NaCl at pH 8.8 with no apolipoprotein

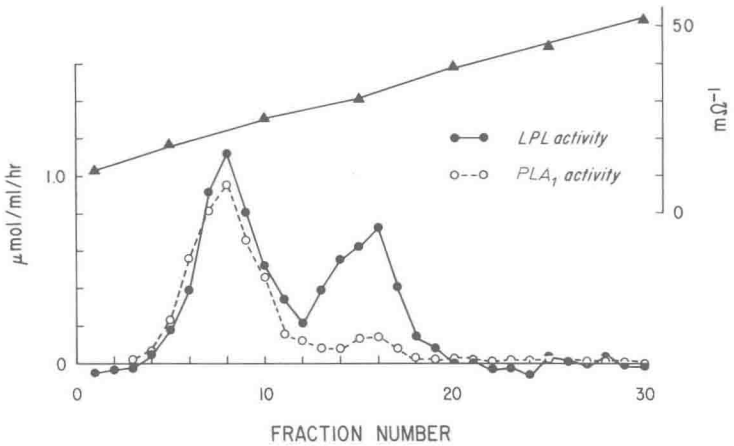

Fig. 2. Separation of postheparin plasma on heparin-Sepharose. Elution of human postheparin plasma with gradient of NaCl. Triglyceride lipase activity was assayed under conditions optimal for LPL (●—●). The phospholipase (PLA_1) was measured using phosphatidylethanolamine as substrate (o---o) as previously described (8). Released free fatty acids from both lipids are given on the left ordinate. The conductivity of the eluting buffer is shown (▲——▲)

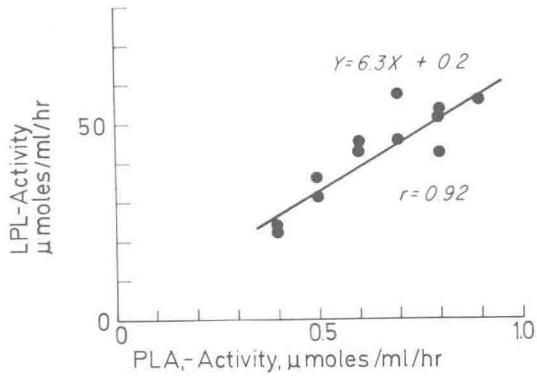

Fig. 3. Postheparin plasma obtained from 12 subjects with normal lipid levels was chromatographed on heparin-Sepharose by stepwise elution with NaCl (14). LPL was assayed as described in Fig. 1

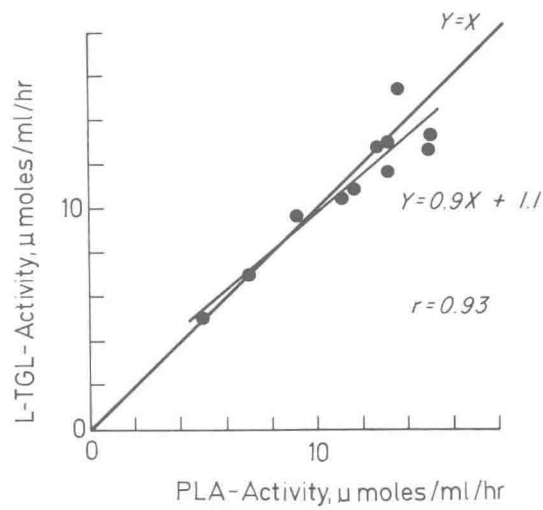

Fig. 4. Relationship between PLA_1 and H-TGL activity in human postheparin plasma. Hepatic lipase (H-TGL) was measured after isolation from same donors as in Fig. 3. Assay conditions were those described in Fig. 1

the latter enzyme. The possibility of a separate monoglyceride hydrolase has been suggested by chromatographic data (10). This enzyme or H-TGL could function to prevent the build-up of plasma monoglyceride which might accumulate as a result of the LPL activity.

The surface coat of all lipoproteins contain phospholipid; therefore the description of a phospholipase A_1 (PLA_1) in PHLA stimulated much interest (11). Hydrolysis of this polar lipid might facilitate access of LPL to the inner droplet of triglyceride and thereby provide for increased rates of hydrolysis. The activity is usually assayed in high concentrations of bile salts at high pH (8.8 - 9.0). The Vmax with phosphatidyl ethanolamine is approximately 25 times greater than that with phosphatidylcholine as substrate. It now seems clear that the H-TGL has all the properties previously described for this phospholipase and is sufficient in quantity to explain most of the PLA_1 activity in PHLA (8). However, recent studies indicate that LPL also has some PLA_1 activity (Fig. 2). The Vmax of LPL is about 6 times

greater as a triglyceride lipase than as a phospholipase (Fig. 3). With H-TGL, the activity is approximately equal (Fig. 4). There is, however, little evidence that the PLA_1 activity of either enzyme plays an important role in lipoprotein clearance.

The thioester of coenzyme A and long-chain fatty acid is hydrolyzed by both H-TGL and LPL (12). Although this lipid is not a common constituent of plasma lipoproteins its flux through the plasma compartment has not been adequately studied and the mechanism of its clearance may be an important physiologic consideration. Using triolein and palmitoyl-CoA as substrates, human H-TGL was found to be 1.4 - 1.6 times more active as a triglyceride hydrolase than as a thioesterase. In similar experiments with human plasma LPL the ratios were 6 to 8. Therefore, in relative terms H-TGL is more active in hydrolyzing palmitoyl-CoA than is LPL.

Lipases and Lipoprotein Clearance

Studies comparing the two triglyceride lipase activities in PHLA are still very limited in number. With an assay utilizing protamine for selective inhibition of LPL, no relationship was found between the level of triglyceride and either the protamine-inhibited (LPL) or protamine-resistent (H-TGL) activity in the subjects studied (13). There was, however, a marked deficiency of LPL in some subjects with familial hyperchylomicronemia. Utilizing heparin affinity chromatography to separate and quantitate the individual enzymes a negative relationship has been found between plasma triglyceride and LPL in subjects with normal triglyceride levels (14). In three subjects studied from two kindred with familial hyperchylomicronemia (type I hyperlipoproteinemia) LPL was not measurable (15). H-TGL, however, was within the normal range. In subjects with elevated VLDL (type IV hyperlipoproteinemia) the mean level of lipoprotein lipase was below that of the normal group but a large overlap of values was noted. The H-TGL did not correlate with LPL values or with plasma levels of lipids.

Function in Tissue

The histochemical evidence of lipolysis in the capillary lumen (16), convincing electron micrographs of adherent and partially digested chylomicra (17), and the rapid appearance of enzyme in heparin-containing tissue perfusates strongly suggest that LPL is located on the luminal surface of capillary endothelial cells. The quantity of the enzyme released appears to relate to the level of circulating triglyceride in normal subjects. In those subjects in whom no LPL is found, chylomicrons are cleared much more slowly but VLDL catabolism is less altered (18).

The normal function of the enzyme on the capillary membrane must depend on the complicated steps of snythesis, secretion, transport across the endothelial cells, and binding at its site of action. In normal individuals, the rate-limiting step in triglyceride clearance is apparently related to the quantity of enzyme bound. In type I hyperlipoproteinemia a failure in any one of these functions could lead to the apparent deficiency in lipoprotein lipase. Since H-TGL is apparently normal in type I and since this enzyme and LPL share a common polypeptide structure with the principal differences found in the carbohydrate component, low levels of LPL may result from failure of glyco-

sylation which in turn could be expressed in failure of secretion or binding.

In subjects with type IV hyperlipoproteinemia normal levels of LPL may simply reflect oversynthesis of VLDL. However, it is also conceivable that the presence of the enzyme in a heparin-releasable form is not sufficient to ensure optimal lipolysis and that factors such as mobility in the membrane or allosteric changes induced by the binding site may be highly relative to the enzyme's function.

The physiologic role of H-TGL remains a mystery. It is possible that this enzyme is located on the hepatocyte surface, removing the small amount of triglyceride left on VLDL and chylomicron remnants after the major digestive process has occurred in the peripheral tissues. If this location were true, the lipoprotein would have to pass into the space of Disse before lipolysis could occur. VLDL would thus have greater access to the enzyme than would the chylomicra, and in type I hyperlipoproteinemia the disparate clearance of these two triglyceride-rich lipoproteins might be explained.

It now seems possible that all the major lipolytic activities described in postheparin plasma can be attributed to lipoprotein lipase secreted by extrahepatic tissues and by an isoenzyme of hepatic origin. At present, the only clear relationship that emerges from the study of plasma lipoproteins and lipolytic activities is that between plasma triglycerides and the triglyceride hydrolase activity of LPL.

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