

Drugs Affecting

Lipid Metabolism X

DRUGS AFFECTING LIPID METABOLISM X

Proceedings of the Xth International Symposium
on Drugs Affecting Lipid Metabolism,

Houston, Texas, November 8-11, 1989

Chairmen: Antonio M. Gotto Jr and Rodolfo Paoletti

Editors:

ANTONIO M. GOTTO JR

*Department of Medicine
Baylor College of Medicine
and
Internal Medicine Service
The Methodist Hospital
Houston, TX, USA*

LOUIS C. SMITH

*Departments of Experimental Medicine, Biochemistry, Cell Biology,
Physiology and Molecular Biophysics
Baylor College of Medicine
Houston, TX, USA*



1990

EXCERPTA MEDICA, Amsterdam - New York - Oxford

© 1990 Elsevier Science Publishers B.V. (Biomedical Division)

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system or transmitted in any form or by any means, electronic, mechanical, photocopying, recording or otherwise without the prior written permission of the publisher, Elsevier Science Publishers B.V., Biomedical Division, P.O. Box 1527, 1000 BM Amsterdam, The Netherlands.

No responsibility is assumed by the Publisher for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions or ideas contained in the material herein. Because of rapid advances in the medical sciences, the Publisher recommends that independent verification of diagnoses and drug dosages should be made.

Special regulations for readers in the USA – This publication has been registered with the Copyright Clearance Center Inc. (CCC), 27 Congress Street, Salem, MA 01970, USA. Information can be obtained from the CCC about conditions under which photocopies of parts of this publication may be made in the USA. All other copyright questions, including photocopying outside the USA, should be referred to the copyright owner, Elsevier Science Publishers B.V., unless otherwise specified.

International Congress Series No. 905
ISBN 0 444 81201 6

This book is printed on acid-free paper.

Published by:
Elsevier Science Publishers B.V.
(Biomedical Division)
P.O. Box 211
1000 AE Amsterdam
The Netherlands

Sole distributors for the USA and Canada:
Elsevier Science Publishing Company Inc.
655 Avenue of the Americas
New York, NY 10010
USA

Printed in The Netherlands

Acknowledgement

We are pleased to acknowledge the support of the Fondazione Giovanni Lorenzini, The Methodist Hospital, and Baylor College of Medicine. We also acknowledge Bristol-Myers Squibb Company, Merck, Sharp & Dohme, Merrell Dow Research Institute, Parke Davis Division of Warner Lambert Company, and Sandoz Pharmaceuticals Corporation for their support of the symposium. We would also like to thank Ms Karena Beerse and colleagues of Elsevier and Ms Anita Cecchin of Baylor College of Medicine for their help in coordinating this text.

CONTENTS

INTRODUCTORY LECTURE

Status of control of atherosclerosis and lipids

A.M. Gotto Jr

3

PLENARY LECTURES

Genetic dissection of complex phenotypes: Conceptual issues in the design of genetic experiments

J.M. Lalouel

11

Metabolism of triglyceride-rich lipoproteins and high density lipoproteins

J.R. Patsch, G. Miesenböck, H. Drexel, A.M. Gotto Jr and

W. Patsch

23

Type III hyperlipoproteinemia: Dominant versus recessive expression of this lipoprotein disorder

R.W. Mahley

29

Drugs affecting hypertriglyceridemia and lipoprotein metabolism

S. Eisenberg and E. Sehayek

35

HMG-CoA REDUCTASE INHIBITORS: A FIVE YEAR BASIC PERSPECTIVE

Role of HMG-CoA reductase inhibitors in preservation of vascular function

A.M. Lefer

45

Metabolic effects of HMG CoA reductase inhibitors in patients with hypercholesterolemia

D.R. Illingworth

49

LIPID ABSORPTION, SYNTHESIS AND SECRETION

Synthesis and secretion of hydroxylated linoleic acid derivatives by human endothelial cells

A.A. Spector, T.L. Kaduce, P.H. Figard and R.L. Leifur

55

Is the oral fat tolerance a marker of lipid risk for atherosclerosis?

S. Martini, G. Baggio, L. Previato, C. Gabelli, S. Pigozzo, C. Corti,

C. Bilato and G. Crepaldi

59

Regulation of eicosanoid synthesis and metabolism by the macrophage-derived foam cell <i>F.J. Field and S.N. Mathur</i>	67
Mechanisms of atheroma macrophage foam cell formation: The role of intracellular lipoprotein-cholesterol metabolism <i>I. Tabas</i>	93

RECEPTORS AND INTRACELLULAR HOMEOSTASIS

Characterization of some mutations of LDL-receptor gene in Italian patients with familial hypercholesterolemia <i>N. Lelli, M.G. Ghisellini, S. Calandra and S. Bertolini</i>	127
Structure and function of the LDL receptor related protein (LRP) <i>K.K. Stanley</i>	133
Two different apolipoprotein-B specific receptors mediate oocyte growth and somatic cholesterol homeostasis in the laying hen <i>W.J. Schneider</i>	137
Mutations of apolipoprotein B that affect plasma cholesterol levels <i>T.L. Innerarity</i>	141

MOLECULAR BIOLOGY OF LIPOPROTEINS

Modulation of apolipoproteins AI, AII and E expression by different cytokines <i>M. Lucero, A. Sidoli, J. Wietzerbin and F.E. Baralle</i>	147
Transcription factor AF-1 interacts with the apo CIII, B and AI promoters <i>T. Leff, A. Melian, B. Ohlsson and P. Gruber</i>	153
Intracellular sterol and apo E biosynthesis <i>G.S. Getz, T. Mazzone, J. Schreiber, K.L. Wyne and L.M. Olson</i>	157
Regulation of hepatic lipoprotein biosynthesis <i>W. Patsch, Y.-C. Lin-Lee, W. Strobl, N. Gorder, A.M. Gotto Jr and J.R. Patsch</i>	161
Regulatory elements of the apolipoprotein E gene and its expression in transgenic mice <i>J.M. Taylor, Y.-K. Paik, D.J. Chang, W.S. Simonet, N. Bucay, T. Leren, D. Walker and S.J. Lauer</i>	165

HDL RECEPTORS AND REVERSE TRANSPORT OF CHOLESTEROL

In vivo evidence for reverse cholesterol transport from liver endothelial cells to parenchymal cells and bile by high density lipoprotein <i>H.F. Bakkeren, F. Kuipers, R.J. Vonk and T.J.C. van Berkel</i>	171
The genetic basis of familial lecithin: cholesterol acyltransferase deficiency <i>J.W. McLean</i>	175

Reassembly of human apo A-I CNBr fragments with DMPC.	
Formation of discoidal particles	
<i>M. Rosseneu, B. Vanloo, J. Morrison, N. Fidge, G. Lorent, R. Brasseur and J.M. Ruysschaert</i>	179
The role of HDL-subclasses in the regulation of cholesterol and phospholipid metabolism in macrophages and its disturbances in Tangier disease and HDL-deficiency with xanthomas	
<i>G. Schmitz, M. Beuck and T. Brünig</i>	183

NATIONAL AND INTERNATIONAL CHOLESTEROL CAMPAIGNS

The U.S.A. National Cholesterol Campaign	
<i>D.S. Goodman</i>	191
A Canadian policy on reducing risk of coronary heart disease	
<i>L. Horlick</i>	197

FRONTIERS IN CHOLESTEROL METABOLISM AND INTERVENTION

A finger protein that binds to the sterol regulatory element: A hypothesis and preliminary cDNA expression studies	
<i>A.J. Lusis, T.B. Rajavashisth, B.-H. Shieh, A.K. Taylor, A. Andalibi, K.L. Svenson and C.H. Warden</i>	201
Molecular cloning of mevalonate kinase and its novel role in regulation of cholesterol biosynthesis	
<i>R.D. Tanaka, L.Y. Lee, B.L. Schafer, J.S. Freudenberger, V.J. Kratunis and S.T. Mosley</i>	205
Design and biological activity of a new class of non-lactone HMG-CoA reductase inhibitors	
<i>D.S. Karanewsky, M.C. Badia, S.A. Biller, C.P. Ciosek, V.C. Dehmelt, B. Delange, L. Duncan, E.M. Gordon, T.W. Harrity, L.N. Lisansky, J. Marretta, L.C. Rich, J.A. Robl, L.M. Simpkins, M.J. Sofia and D.A. Slusarchyk</i>	209
Squalene synthetase inhibition: Progress towards a new approach for the regulation of cholesterol biosynthesis	
<i>S.A. Biller, C. Forster, E.M. Gordon, T. Harrity, L.C. Rich, J. Marretta, W.A. Scott and C.P. Ciosek Jr</i>	213

FIBRATES

Rationale for fibric acid use in treating familial combined hyperlipidemia (FCHL)	
<i>R.H. Knopp</i>	219

Ciprofibrate treatment in hyperlipidemic patients. Italian multicenter study

E. Manzato, G. Descovich, F.S. Feruglio, A. Ventura and G. Crepaldi

225

Fibrates and triglyceride metabolism

P. Schwandt

229

CYCLOOXYGENASE/LIPOXYGENASE

Platelet reactivity and thromboxane formation in type IIa hypercholesterolemia and its modification by cholesterol-lowering agents

K. Schrör

239

DIETS

Apoprotein E phenotype and metabolic lipid responses to dietary fat modification

T.A. Miettinen, H. Vanhanen, H. Gylling and A. Ollus

245

Monounsaturated fatty acids in the diet and plasma lipoproteins

R. Carmena, M. de Oya, J.F. Ascaso, P. Mata, S. Serrano,

L. Alvarez-Sala, F.J. Martinez-Valls and M.J. Rubio

249

Nutritional strategies for preventing atherosclerosis and its complications

P.J. Nestel

253

MODIFIED LIPOPROTEINS AND THEIR RECEPTORS

Monocyte-macrophage receptor pathway for abnormal triglyceride-rich lipoproteins

S.H. Gianturco, A.H.-Y. Lin, M.P. Ramprasad, R. Song and W.A. Bradley

261

Binding of oxidized low density lipoprotein (Ox-LDL) to reduced hepatic receptors for acetyl-LDL and maleylated albumin (Mal-BSA)

H.A. Dresel, E. Ottnad, R. Ziegler, E. Friedrich and H. Sinn

265

Effect of simvastatin in subjects with binding-defective low density lipoprotein

A. Corsini, L. Romano, A. Granata, C. Romano, R. Fumagalli and A.L. Catapano

269

ANTIOXIDANT DRUGS

Probucol: A cholesterol lowering drug with multiple pharmacological effects for reducing atherosclerosis

R.L. Jackson, L.R. McLean, A.L. Akeson, G. Ku, J.W. Barnhart and S.J.T. Mao

279

Probucol reduces lipid deposition in vivo in atherosclerotic lesions of rabbits with hypercholesterolemia of either genetic or dietary origin	
<i>A. Daugherty</i>	283
Effects of antioxidants on oxidative modification of LDL	
<i>M. Dieber-Rotheneder, G. Striegl and H. Esterbauer</i>	287

NONINVASIVE AND NONSURGICAL TECHNIQUES

Metabolic imaging of arterial lesions with lipoprotein-based synthetic oligonucleotides	
<i>R.S. Lees and A.M. Lees</i>	295
Maximal therapy of severe hypercholesterolemia in CHD-patients: Long term experience with the HELP LDL-apheresis in combination with HMG-CoA-reductase inhibitors	
<i>D. Seidel, J. Thiery, H.-G. Fieseler, P. Schuff-Werner, T. Eisenhauer and V.W. Armstrong</i>	299
Carotid atherosclerosis B-mode ultrasonography endpoints in interventional trials	
<i>M.F. Mercuri, M.G. Bond, H.L. Strickland and S.K. Wilmoth</i>	307

CLINICAL TRIALS METHODOLOGY AND ENDPOINTS OF MEASUREMENT

Selection of a primary endpoint – A diagnostic, practical and financial dilemma	
<i>G. Walldius</i>	313
Quantitative imaging of human liver LDL-receptor in vivo	
<i>H. Sinzinger, I. Virgolini, G. Lupattelli and F. Rauscha</i>	319

ω -3 AND ω -6 FATTY ACIDS

Dietary polyunsaturated fatty acids, plasma lipids and cell function	
<i>C. Galli and E. Tremoli</i>	331
Effect of eicosapentaenoic acid on triglyceride transport in CaCo-2 cells	
<i>S. Murthy, E. Albright, S. Mathur and F.J. Field</i>	337

INTRACELLULAR REGULATORY EFFECTS OF CHOLESTEROL

Two promoters in the rat farnesyl pyrophosphate (FPP) synthetase gene generate somatic and testis specific transcripts	
<i>C.F. Clarke, J.H. Teruya, S.Y. Kutsunai, D.H. Spear and P.A. Edwards</i>	359
Hypobetalipoproteinemia associated with two truncated forms of apoB in a U.S.A. kindred	
<i>G. Schonfeld, E.S. Krul, P. Talmud, A. Daugherty and S.E. Humphries</i>	363

WHAT IS THE FUTURE OF CHD PREVENTION AND THE ROLE OF LIPID REGULATION

Availability of lipid lowering drugs in Canada

O.J. Lucis

369

ATHEROGENESIS: PREVENTION AND CONTROL

Therapeutic reduction of cholesterol accumulation

G.R. Thompson and I. Michishita

377

Compliance measures and new lesion counts in trials of atherosclerosis regression

C.-R. Liu, D.H. Blankenhorn and R.H. Selzer

381

REGRESSION: ANIMAL AND HUMAN STUDIES

Nonhuman primate studies on plasma cholesterol lowering and regression of atherosclerosis

T.B. Clarkson

395

Ultrastructural morphometric signs of platelet activation and their reversal after plasma exchange and LDL-apheresis in hypercholesterolemic type IIa patients

G. Weber, G. Bianciardi, P. Tanganelli, N. Scarpato, A. Gnasso, A. Postiglione and M. Mancini

399

Lowering cholesterol by intensive drug and apheresis treatment results in the regression of atherosclerosis

A. Yamamoto and B.-I. Kishino

407

Radiological imaging of atherosclerosis in human regression studies

U. Erikson, S. Nilsson and G. Ruhn

411

ANTIDIABETIC DRUGS AND LIPIDS

Effect of insulin treatment on serum lipoprotein composition in diabetic patients

M. Mancini, G. Romano, L. Patti, A. Rivellese and G. Riccardi

417

Diabetes, hypertriglyceridemia and atherosclerosis

G. Steiner

421

Hypolipidemic therapy for dyslipidemia in patients with non-insulin-dependent diabetes mellitus

A. Garg and S.M. Grundy

427

THROMBOSIS AND FIBRINOLYSIS

Control of blood cell and vessel reactivity in vascular diseases

A.J. Marcus, L.B. Safier, K.A. Hajjar, H.L. Ullman, N. Islam, M.J. Broekman, J. Valles, M.T. Santos, A.M. Eiroa and D.P. Hajjar

433

- Lipoprotein (a) has serine proteinase activity that can cleave fibronectin
C. Ehnholm, M. Jauhiainen, J. Metso, E.-M. Salonen and A. Vaheri 435

ACAT INHIBITORS, RESINS, AND INTESTINAL LIPID ABSORPTION

- Cholesteryl ester metabolism in the hamster liver
K.E. Suckling, S. Black, B. Jackson, A. Gee, B. Ochoa and M. Martinez-Cayuela 443
- Trisubstituted ureas (TSU) are potent inhibitors of ACAT and dietary cholesterol absorption
E.E. Largis and A.S. Katocs Jr 447
- The water soluble chitosan derivative CP-88488 shows a different activity profile vs cholestyramine
C.R. Sirtori, H.J. Harwood Jr., C.E. Chandler, L.D. Pellarin and F.W. Bangerter 451

AN HDL WORKSHOP: AN UPDATE ON THE INTERRELATIONSHIP OF HDL AND ATHEROSCLEROSIS

- An historical overview of the HDL hypothesis
A.M. Gotto Jr 459
- Drugs that affect HDL metabolism
J. Johansson, J. Mølgaard, G. Wahlberg, G. Walldius and A.G. Olsson 465
- HDL levels and their significance in the Helsinki heart study
J.K. Huttunen, M. Mänttari, P. Koskinen, V. Manninen, O.P. Heinonen and M.H. Frick 471

ANIMAL MODELS

- New horizons and new compromises: A perspective on small animal models of lipoprotein metabolism
J.R. Paterniti Jr., J.B. Eskesen, D.S. France, T.E. Hughes, J. Babiak, M. Swanson, J.A. Spirito, R. Miserendino, M.A. Islam, K. Burki and D.B. Weinstein 477
- Atherosclerosis induced in rabbits by semipurified diets
D. Kritchevsky 481
- Old world monkeys and atherosclerosis research
M.L. Armstrong, D.D. Heistad, D.G. Harrison and J.A. Lopez Jr 485
- Dietary polyunsaturated fat and cholesterol effects on plasma lipoprotein metabolism during atherosclerosis development
L.L. Rudel, F.L. Johnson, M. Sorci-Thomas and D.L. Williams 489

INTRAVASCULAR DYNAMICS OF LIPIDS AND DRUGS

- Modified lipoproteins during regression of atherosclerosis in pigs fed with fish oil-derived fatty acids
A. van Tol, T. van Gent, L.M.A. Sassen, J.M.J. Lamers and P.D. Verdouw 495
- Drugs and lipoprotein heterogeneity
J. Shepherd, B. Griffin, M.J. Caslake, C.J. Packard, B. Yip and A. Gaw 503
- Long-term treatment of primary hypercholesterolemia with Simvastatin or Pravastatin: Australian experience
L.A. Simons 507

CELL BIOLOGY, ATHEROSCLEROSIS AND Ca^{++} ANTAGONISTS

- Calcium antagonists and cellular lipid metabolism
F. Bernini, S. Bellosta, S.M. Bertulli and R. Fumagalli 513

TRIGLYCERIDE METABOLISM AND FATTY ACID UTILIZATION

- Lipoprotein lipase: Evolution and structure-function relationships
C.F. Semenkovich, C.-C. Luo, W.-H. Li, L.C. Smith and L. Chan 521
- Hepatic lipase and lipoprotein lipase: Molecular insights
M.C. Schotz, T.G. Kirchgessner, D. Ameis, J.-C. Chaut, G. Stahnke, J. Kobayashi, H. Will and A.J. Lusis 525
- Mechanisms for regulation of lipoprotein lipase
T. Olivecrona, G. Bengtsson-Olivecrona and S. Vilaró 529
- Human lipoprotein lipase: From gene to protein
M.R. Hayden and J.D. Brunzell 535
- Inactivation of pancreatic and gastric lipases: A selective suicide by interfacial enzyme adsorption
R. Verger, Y. Gargouri, H. Moreau, S. Ransac, A. Moulin and C. Riviere 539

CONTROL OF LIPID DISORDERS IN LATIN AMERICA

- Primary hypoalphalipoproteinemia in Mexico City: Genetic and biochemical profiles of 40 cases with premature atherosclerosis
M. Ahumada, I. Lerman and C. Posadas 545
- Hypercholesterolemia and coronary heart disease in Mexico: A preliminary report
G. Lerman, A.J. Sepúlveda, C.R. Tapia, L.C. Magos and H.R. Fernández 553

OXYSTEROLS AND CHOLESTEROL METABOLISM

Rapid suppression of bile acid synthesis by drugs which inhibit cholesterol synthesis

Z.R. Vlahcevic, W.M. Pandak, D.M. Heuman and P.B. Hylemon

563

Index of authors

573

INTRODUCTORY LECTURE

STATUS OF CONTROL OF ATHEROSCLEROSIS AND LIPIDS

Antonio M. Gotto, Jr., M.D., D.Phil.
Chairman, Department of Medicine
Baylor College of Medicine, and
Chief, Internal Medicine Service
The Methodist Hospital, Houston

The cholesterol connection to coronary heart disease (CHD), known as the lipid hypothesis, is at the forefront of medical interest. This interest is due in part to recent studies which have shown that cholesterol modification, through diet or pharmacologic therapy, can reduce CHD risk. The interest is also due to the 1987 launch of the National Cholesterol Education Program (NCEP), a joint effort by the National Institutes of Health and 37 public and private health organizations to inform the public about the need for cholesterol management. In 1988, the NCEP recommended that all adults over age 20 know their cholesterol level. It also recommended three specific treatment algorithms based on a patient's total- and LDL-cholesterol measurements.

The efforts of the NCEP, however, have come under recent criticism by popular magazine writers and by a small group of physicians. They claim that the connection between cholesterol and CHD is not well defined, that lowering cholesterol does not extend life, that low-cholesterol diets do little to reduce the risk of CHD, and that the NCEP recommendations are not applicable to women or the elderly. Unfortunately, the critics' well-publicized claims have led many patients to disregard the NCEP's recommendations. Some patients have even discontinued their cholesterol-lowering treatment because of the critics' claims.

Physicians must now separate the critics' **cholesterol myths** from the **cholesterol facts**. To help them do this, the American Heart Association and the National Heart, Lung, and Blood Institute commissioned a special report called 'The Cholesterol Facts.' It counters the critics' assertions with documented evidence of the lipid hypothesis. A brief synopsis of the report follows:

**Is high serum cholesterol a risk factor for CHD, and
will lowering it help prevent CHD?**

Epidemiologic, clinical, genetic, and laboratory animal studies all demonstrate that high serum cholesterol levels predispose a patient to premature CHD.

The strongest support for the lipid hypothesis comes from the Lipid Research Clinics Coronary Primary Prevention Trial (CPPT). More than 3,800 asymptomatic, hypercholesterolemic middle-aged men were placed on low-fat diets and then randomized and treated with either a placebo or cholestyramine. Over the seven-year trial, the cholestyramine group reduced its total and LDL cholesterol levels by averages of 9% and 12% respectively, when compared to the placebo group. In turn, the cholestyramine group had 19% fewer CHD events than the placebo group. These findings indicated a 1:2 ratio between the degree of total cholesterol lowering and CHD reduction.

The more than 4,000 subjects in the five-year Helsinki Heart Study, a double-blinded, randomized trial, were also asymptomatic, middle-aged men with hypercholesterolemia. Men treated with gemfibrozil lowered their total cholesterol by 10%, their LDL by 11%, their triglycerides by 35%, and increased their HDL by 11%, when compared to the placebo group.

Based on the 1:2 ratio of the CPPT, the Helsinki gemfibrozil group was expected to have 20% fewer CHD events than the placebo group since their total cholesterol fell by 20% more than that of the placebo group. Instead, they experienced 34% fewer cardiac deaths and nonfatal myocardial infarctions. The results suggested that a combination therapy of lowering total and LDL cholesterol, while raising HDL cholesterol, exerts a stronger effect on CHD incidence than lowering LDL cholesterol alone.

Will low-cholesterol diets reduce CHD risk?