Drugs Affecting Lipid Metabolism

Edited by
R. Paoletti
D. Kritchevsky, W. L. Holmes

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Preface

The recent symposium and the appearance of this new book on *Drugs Affecting Lipid Metabolism* take place at a very unusual time for the development of this area.

After the publication and wide acceptance of the results of the cholestyramine study by the Lipid Clinics in the USA, showing for the first time a direct association between drug induced reduction of plasma levels of total and LDL cholesterol and coronary heart disease in a high risk population, an unparalleled interest in drugs and other procedures able to control plasma cholesterol levels has been activated.

Two other significant events occurred during 1986 and 1987: the availability of compact instruments for the immediate determination of total cholesterol in plasma or total blood and the developments of new agents such as the inhibitors of HMG-CoA (hydroxymethyl-glutaryl CoA) reductase and ACAT inhibitors, with potentially great effect on plasma lipid levels after oral administration.

These new advances, together with the combined efforts of cell biologists and lipoprotein chemists, have set the pace for an exciting period of research and clinical applications of diets and drugs affecting lipids.

This volume, which includes the work of many of the leading world laboratories, represents an authoritative and up-to-date appraisal of the status of the art and a stimulus to future research at laboratory and clinical level in an area of opportunity for clinical and preventive medicine.

Milan, October 1987 Rodolfo Paoletti

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The Editors

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Contents

Relationship of Cholesterol to DNA Synthesis in Normal and Cancerous Cells

M. D. SIPERSTEIN, H. DOVALE, and J. R. SILBER [1]

It has been known since 1950 that there is a striking correlation between the rate at which acetate is converted to cholesterol and the rate of cell growth. Specifically, in tissues such as the kidney, cell replication is very slow and such tissues have low rates of cholesterol synthesis. By contrast, baby brain and intestine replicate at rapid rates and have active cholesterol synthesis. As we showed some years ago, the very rapid cell growth of regenerating liver is accompanied by one of the highest rates of cholesterolgenesis seen in mammalian cells (1).

Our interest in the relation between cell replication and cholesterol biosynthesis developed from two observations. One was the finding that the primary site of feedback control of cholesterol synthesis is located at the synthesis of mevalonate (2,3). Second was our initial observation that this feedback control of mevalonic acid, at least in vivo, is consistently impaired or completed deleted in a series of malignant tumors (1,4,5). In contrast to the liver, where the feeding of cholesterol leads to a marked decrease in the conversion of acetate to cholesterol and a comparable decrease in the activity of HMG CoA reductase, in the slowly growing hepatoma 9121 feeding cholesterol does not inhibit either cholesterogenesis or HMG CoA reductase activity (Table 1) (6,7). Similar data have been reported by Goldfarb and Pitot (7).

Table 1. Absence of feedback control of HMG CoA reductase in hepatoma 9121

Tissue	Diet	($2\text{-}^{14}C$) Acetate converted to cholesterol mμmol g^{-1} h^{-1}	β-hydroxy-β-methylglutaryl CoA reductase mμmol g^{-1} h^{-1}
Liver	Low cholesterol	45	0.77 ± 0.11
	5% cholesterol	0.8	0.007 ± 0.01
Hepatoma	Low cholesterol	46	1.34 ± 0.14
9121	5% cholesterol	96	1.69 ± 0.17

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Table 2. Absence of cholesterol feedback control in rat hepatomas

Tissue	Diet: Normal Acetate → Chol[a]	Diet: Cholesterol 5% Acetate → Chol[a]
Liver	8	0.02
Hepatomas		
9618A	152	126
9633	72	54
7787	33	32
9121	27	25
5121	9	7
7795	6	7
7793	3	4
7794A	7	18
7316A	4	8
7800	7	9
H-35	6	9
7288C	0.9	1
3924A	0.5	0.6
3683	1	3

[a] nmol 2-14 C acetate g^{-1} h^{-1}.

This phenomenon can be demonstrated in a variety of minimal deviation hepatomas. As shown by the data in Table 2, in contrast to the marked decrease in the conversion of acetate to cholesterol characteristic of the livers of animals fed cholesterol, cholesterol feeding consistently has no significant effect upon cholesterol synthesis in hepatomas. Loss of cholesterol feedback control has been shown to occur in nonhepatic tumors (8) and has been confirmed and extended by a number of investigators (9–12). Moreover, loss of the cholesterol feedback system can be demonstrated even in the precancerous state (13,14). For example, feeding aflatoxin to a rat for a period of only 2 days, led to complete loss of feedback control of cholesterol synthesis and of mevalonate synthesis (15). This observation, too, has been confirmed with a wide variety of cancer-producing agents, primarily by Sabine's laboratory (16–18).

These observations raised the question of what might be the role of cholesterol synthesis in both normal and abnormal cell growth. It is known that cholesterol is required for cell membrane synthesis, and it was shown initially by Chen and Kandutsch (19,20) and by Brown and Goldstein (21) that treating cells in tissue culture with hydroxysterols, which inhibit sterol synthesis by blocking HMG CoA reductase, will also inhibit cell growth. This inhibition could be reversed by adding cholesterol in the form of lipoprotein, a finding that logically led to the conclusion that hydroxysterols prevent cell proliferation by depleting the cell of cholesterol.

Because of our earlier interest in the control of mevalonic acid synthesis, we decided to look at the question of whether mevalonic acid, independent of its function