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Potential therapeutics for obesity and atherosclerosis: Inhibitors of neutral lipid metabolism from microorganisms

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Abstract

Diacylglycerol acyltransferase (DGAT) and acyl-CoA: cholesterol acyltransferase (ACAT) are the enzymes that catalyze the final reactions of triacylgycerol (TG) and cholesteryl ester (CE) synthesis, and accumulation of TG and CE in adipocytes and arteries causes obesity and atherosclerosis, respectively. Therefore, DGAT and ACAT have been viewed as potential therapeutic targets for these diseases. From the screening program for DGAT inhibitors, new compounds were discovered from fungal and plant extracts, and are expected to provide leads for drug development. From the screening programs for ACAT inhibitors and lipid droplet synthesis inhibitors, new compounds with chemical structures different from those of known synthetic inhibitors were discovered from the cultures of fungal and actinomycete strains. Among them, fungal beauveriolide III rather selectively inhibited ACAT1 isozyme, while fungal pyripyropene A was found to be a highly selective inhibitor of ACAT2 isozyme. Both inhibitors proved orally active in in vivo models. Furthermore, a library of beauveriolide and pyripyropene analogs was prepared by combinatorial and semisynthetic methods, respectively. The future prospects of these inhibitors are discussed.

Keywords: Acyl-CoA; Diacylglycerol; Cholesterol; Acyltransferase; DGAT; ACAT; Isozymes; Microbial inhibitor

Abbreviations: DGAT, Diacylglycerol acyltransferase; ACAT, Acyl-CoA: cholesterol acyltransferase; TG, Triacylglycerol; CE, Cholesteryl ester; PC, Phosphatidylcholine; PE, phosphatidylethanolamine; ER, endoplasmic reticulum.

Contents

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1. Introduction

Neutral lipids, triacylglycerol or triglyceride (TG) and cholesteryl ester (CE), are the final storage forms of free long-chain fatty acid and cholesterol in mammals. Excessive accumulation of neutral lipids due to a fat-rich diet or sedentary lifestyle causes obesity and atherosclerosis. Namely, TG accumulates in adipocytes in obesity, and CE accumulates in arteries (macrophages and smooth muscle cells) in atherosclerosis. These conditions contribute to lifestyle-related diseases and metabolic syndrome, to which much attention has been paid recently because of their current importance in health care.

The final enzymes involved in TG and CE biosyntheses are diacylglycerol acyltransferase (acyl-CoA:1,2-diacyl-*sn*-glycerol *O*-acyltransferase, DGAT, EC 2.3.1.20) and acyl-CoA: cholesterol acyltransferase (ACAT, EC 2.3.1.26), respectively. They are membrane proteins of endoplasmic reticulum (ER), and difficult to purify to homogeneity. In spite of the lack of detailed biochemical and structural information about the enzymes, the DGAT and ACAT genes have been identified, and knowledge about the functions of DGAT and ACAT in mammals has accumulated. Focusing on DGAT and ACAT as potential targets for the prevention or treatment of obesity and atherosclerosis, this review will describe DGAT and ACAT inhibitors from microorganisms and their future prospects.

2. Diacylglycerol acyltransferase

TG synthesis in mammals is important in many processes, including lactation, energy storage in adipose tissue and muscle, fat absorption in the intestine, and the assembly of lipoprotein particles in the liver and small intestine. Excess accumulation of TG in certain organs and tissues causes obesity, fatty liver and hypertriglyceridemia. Obesity can be recognized as an energy balance disorder-energy input exceeds energy output. Recent medications approved for the treatment of obesity attempt to restore energy balance by reducing energy input — by suppressing appetite or inhibiting lipid lipase to interfere with lipid absorption from the small intestine.

One potential strategy for the treatment of obesity is to block TG synthesis. As shown in Fig. 1, TG is produced by two pathways, the major glycerol phosphate pathway and the minor monoacylglycerol pathway. DGAT, which catalyzes acyl residue transfer from acyl-CoA to diacylglycerol to form TG, is the enzyme catalyzing the final step common to both pathways, and is exclusively involved in triacylglycerol formation (Bell & Coleman, 1980; Lehner & Kuksis, 1996). Therefore, DGAT is considered a potential target of inhibition for the control of obesity and other disorders. However, only a few DGAT inhibitors have been reported (Tomoda et al., 1995a; Tabata et al., 1997; Ōmura et al., 1999; Casaschi et al., 2004; Lee et al., 2004).

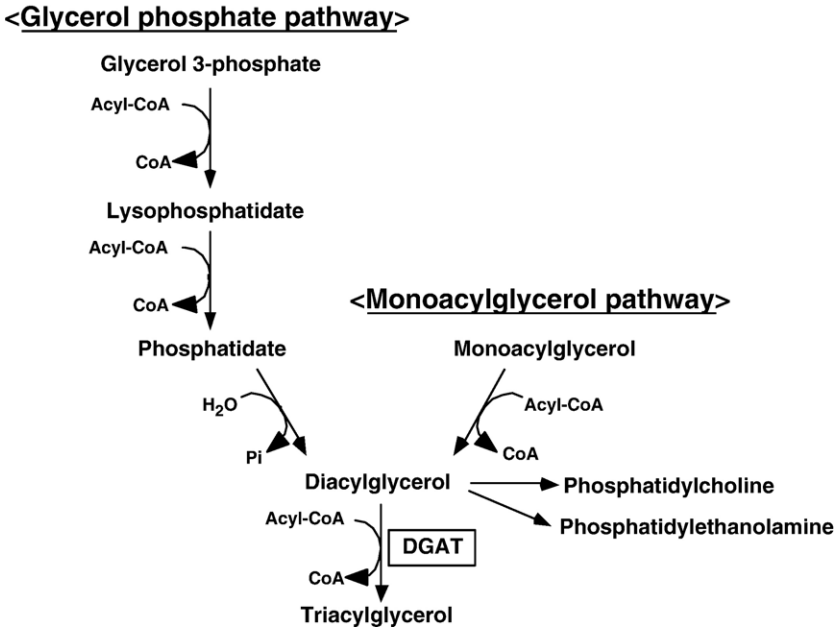

Fig. 1. Biosynthetic pathways of triacylglycerol. In the glycerol phosphate pathway, two acyl-CoAs are sequentially added to glycerol-3-phosphate to form phosphatidate, which is dephosphorylated to yield diacylglycerol. In the monoacylglycerol pathway, dietary monoacylglycerol undergoes acylation in enterocytes of the small intestine to yield diacylglycerol.