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(54) Title: A METHOD OF INHIBITING OR TREATING PHYTOSTEROLEMIA WITH AN MTP INHIBITOR

(57) Abstract

A method is provided for inhibiting onset of or treating phytosterolemia by administering to a patient an MTP inhibitor, alone or optionally, in combination with another cholesterol lowering drug, such as pravastatin.

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A METHOD OF INHIBITING OR TREATING PHYTOSTEROLEMIA WITH AN MTP INHIBITOR

Field of the Invention

The present invention related to a method for inhibiting onset of or treating phytosterolemia, by administering an MTP inhibitor alone or in combination with another cholesterol lowering drug, such as pravastatin.

Background of the Invention

As indicated in Scriver, C.R. et al "Metabolic Basis of Inherited Diseases" Vol. II (1995), Chap. 65, Inborn Errors in Bile Acid Biosynthesis and Storage of Sterols Other than Cholesterol, Bjorkhem, I. and Boberg, K.M., pp. 2073-2099, phytosterolemia (also referred to as sitosterolemia) is a rare inherited sterol storage disease involving increased intestinal absorption of phytosterol or shellfish sterols and decreased fecal secretion. It is characterized by "tendon and tuberous xanthomas and by a strong predisposition to premature coronary atherosclerosis.... Increased amounts of phytosterols (plant sterols), such as sitosterol and campesterol and their 5α-stanols, are found in blood, plasma, erythrocytes, and different tissues, especially in the xanthomas and arteries of affected subjects. Increased serum cholesterol and cholesterol have also been found in many patients." (p. 2073)

Patients afflicted with phytosterolemia have been found to have an increased incidence of coronary heart disease at an early age most likely due to early development of atherosclerosis at an early age. Bjorkhem et al, supra, indicate at page 2090 that "the mechanism behind the atherosclerosis is unexplained, but a high content of plant sterols in the circulating lipoproteins might promote their deposition in the arterial wall."

The microsomal triglyceride transfer protein (MTP) catalyzes the transport of triglyceride (TG), cholesteryl ester (CE), and phosphatidylcholine (PC) between small unilamellar vesicles (SUV). Wetterau & Zilversmit, Chem. Phys. Lipids 38, 205-22 (1985). When transfer rates are expressed as the percent of the donor lipid transferred per time, MTP expresses a distinct preference for neutral lipid transport (TG and CE), relative to phospholipid transport. The microsomal triglyceride transfer protein from bovine liver has been isolated and extensively characterized (1). This has led to the cloning of cDNA expressing the protein from several species, including humans (2). MTP is composed of two subunits. The small subunit is the previously characterized multifunctional protein, protein disulfide isomerase. This is supported by biochemical analysis of the protein (3) as well as co-expression studies performed in insect Sf9 cells using the baculovirus expression system. Expression of soluble active MTP requires the co-expression of PDI and the unique large subunit of MTP (4).

1: Wetterau, J.R. and Zilversmit, D.B. (1985) Chem. Phys. Lipids 38, 205-222.

Wetterau, J.R., et al, (1990) J. Biol. Chem. 265, 9800-9807.

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Atzel, A., and Wetterau, J.R. (1994) Biochemistry 33, 15382-15388.

Jamil, H., et al, (1995) J. Biol. Chem. 270, 6549-6554.

2. Sharp, D. et al, (1993) Nature 365, 65-69.

Lin, M.C.M., et al, J. Biol. Chem. 269, 29138-29145.

Nakamuta, M., et al, (1996) Genomics 33, 313-316.

3. Wetterau, J.R., et al, (1990) J. Biol. Chem. 265, 9800-9807.

Wetterau, J.R., et al, (1991) Biochemistry 30, 9728-9735.

4. Ricci, B., et al, (1995) J. Biol. Chem. 270, 14281-14285.

In vitro, MTP catalyzes the transport of lipid molecules between phospholipid membranes. Presumably, it plays a similar role in vivo, and thus plays some role in lipid metabolism. The subcellular (lumen of the microsomal fraction) and tissue distribution (liver and intestine) of MTP have led to speculation that it plays a role in the assembly of plasma lipoproteins, as these are the sites of plasma lipoprotein assembly. Wetterau & Zilversmit, Biochem. Biophys. Acta 875, 610-7 (1986). The ability of MTP to catalyze the transport of TG between membranes is consistent with this hypothesis, and suggests that MTP may catalyze the transport of TG from its site of synthesis in the endoplasmic reticulum (ER) membrane to nascent lipoprotein particles within the lumen of the ER.

Abetalipoproteinemia is an autosomal recessive disease characterized by a virtual absence of plasma lipoproteins which contain apolipoprotein B (apoB). Kane & Havel in The Metabolic Basis of Inherited Disease, Sixth edition, 1139-64 (1989). Plasma TG levels may be as low as a few mg/dL, and they fail to rise after fat ingestion. Plasma cholesterol levels are often only 20-45 mg/dL. These abnormalities are the result of a genetic defect in the assembly and/or secretion of very low density lipoproteins (VLDL) in the liver and chylomicrons in the intestine. The molecular basis for this defect had not been previously determined. In subjects examined, triglyceride, phospholipid, and cholesterol synthesis appear normal. At autopsy, subjects are free of

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