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(54) DIMINUTION DES CONCENTRATIONS DE LIPOPROTEINE(A) DANS LE SANG
(54) LOWERING BLOOD LEVELS OF LIPOPROTEIN(A)

(57)

The invention relates to methods of lowering blood levels of lipoprotein(a) in a mammal which comprises administering to a mammal in need thereof a lipoprotein(a) blood level-lowering amount of an apolipoprotein B secretion/microsomal triglyceride transfer protein inhibitor.

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(54) **LOWERING BLOOD LEVELS OF LIPOPROTEIN(a)**

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ABSTRACT

The invention relates to methods of lowering blood levels of lipoprotein(a) in a mammal which comprises administering to a mammal in need thereof a lipoprotein(a) blood level-lowering amount of an apolipoprotein B secretion/microsomal triglyceride transfer protein inhibitor.

LOWERING BLOOD LEVELS OF LIPOPROTEIN(a)

Background Of The Invention

The glycoprotein apolipoprotein (a) (apo(a)) is synthesized and secreted from hepatic cells and, in humans, circulates largely in association with low density lipoprotein (LDL) in the form of a hybrid lipoprotein referred to as Lp(a). The association between apo(a) and the major protein molety of LDL, namely apolipoprotein B100 (apo B100), is mediated through covalent linkage of a single unpaired cysteine residue in apo(a) to a complimentary unpaired cysteine residue in the extreme carboxyl terminus of apo B100.

Interest in the biology of this lipoprotein species is driven by the observation that elevated levels of Lp(a) in humans is associated with an increased risk for atherosclerotic heart and vascular disease. The lowering of Lp(a) levels, however, has proven problematic since various conventional methods that are effective in reducing levels of LDL are not as efficacious or consistent in lowering levels of Lp(a). For example, it has been reported that neomycin, alone or in combination with niacin, is effective in reducing Lp(a) levels when administered over a period of several weeks to years. See Spinler, et al., J. Ann. Pharmacother., 28, 343 (1994). The administration of high doses of niacin and neomycin, however, limits the desirability of this regimen due to many undesirable clinical side-effects. Alternatively, oral doses of fosinopril, an angiotensin-converting enzyme inhibitor, have been demonstrated to lower Lp(a) levels after 12 weeks of treatment, however, Lp(a) reduction was significant only in patients that showed improvement in renal function and, therefore, the Lp(a) lowering ability of fosinopril may simply be attributable to the indirect consequence of improved kidney function. See Keilani, et al., Ann. Inter. Med., 118, 246 (1993). Additionally, certain steroidal hormones, estrogen for example, are known to down-regulate Lp(a) levels. See, for example, Frazer, et al., Nature Genet., 9, 424 (1985). However, estrogen therapy alone is associated with an increased risk of endometrial carcinoma and, for this reason, estrogen is normally administered in combination with progesterone. Although short-term treatment with this estrogen/progesterone combination is an effective therapeutic strategy for reducing Lp(a) levels, long-term treatment, i.e. six months or more, does not result in the same degree of decreased inhibition as that observed for treatment with estrogen alone. See Soma, et al., Arch.

Internal. Med., 153, 1462 (1993) and Soma, et al., Chem. Phys. Lipids, 345, 67 (1994). Furthermore, LDL apheresis has been shown to be an effective means for lowering Lp(a) levels. See Koizumi, et al., Atherosclerosis, 100, 65 (1993). However, apheresis is an invasive approach requiring weekly treatments and, therefore, is not regarded as a current treatment of choice. Accordingly, improved methods of inhibiting Lp(a), or formation of the precursors thereof, will have utility in the treatment of conditions and diseases arising from hyperlipoproteinemia, including, for example, atherosclerosis, premature myocardial infarction, stroke, restenosis following coronary bypass surgery and so forth.

Microsomal triglyceride transfer protein (MTP) is known to mediate the transport of triglyceride, cholesteryl ester and phospholipids and has been implicated as a mediator in the assembly of apolipoprotein B containing lipoproteins, chylomicrons and VLDL (very low density lipoprotein). Specifically, 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. The ability of MTP to catalyze the transport of triglyceride between membranes is consistent with this speculation and suggests that MTP may catalyze the transport of triglyceride from its site of synthesis in the endoplasmic reticulum membrane to nascent lipoprotein particles within the lumen of the endoplasmic reticulum. Accordingly, compounds that inhibit MTP and/or otherwise inhibit apo B secretion are useful in the treatment of atherosclerosis and other conditions related thereto. Such compounds are also useful in the treatment of other diseases or conditions in which, by inhibiting MTP and/or apo B secretion, serum cholesterol and triglyceride levels may be reduced. Such conditions may include, for example, hypercholesterolemia, hypertriglyceridemia, pancreatitis, obesity and hypercholesterolemia, hypertriglyceridemia and hyperlipidemia associated with pancreatitis, obesity and diabetes. For a detailed discussion see, for example, Wetterau et al., Science, 258, 999-1001 (1992) and Wetterau et al., Biochem. Biophys. Acta., 875, 610-617 (1986).

While the precise mechanisms governing blood levels of Lp(a) are presently unknown, there is evidence to suggest that Lp(a) levels are regulated at the level of synthesis rather than catabolism. Accordingly, because it is known that inhibition of hepatic secretion of VLDL and apolipoprotein B (apo B) results in the pre-secretory degradation of apo B and concomitant decrease in hepatic apo B levels and because

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