Lipoprotein Lipase Activator NO-1886

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ABSTRACT

Lipoprotein lipase (LPL) is a rate-limiting enzyme that hydrolyzes circulating triglyceride-rich lipoproteins such as very low-density lipoproteins and chylomicrons. A decrease in LPL activity is associated with an increase in plasma triglycerides (TG) and a decrease in plasma high-density lipoprotein cholesterol (HDL-C). The increase in plasma TG and decrease in plasma HDL-C are risk factors for cardiovascular disease. Tsutsumi et al. hypothesized that elevating LPL activity would cause a reduction of plasma TG and an increase in plasma HDL-C, resulting in protection against the development of atherosclerosis. To test this hypothesis, Otsuka Pharmaceutical Factory, Inc. synthesized the LPL activator NO-1886.

NO-1886 increased LPL mRNA and LPL activity in adipose tissue, myocardium and skeletal muscle, resulting in an elevation of postheparin plasma LPL activity and LPL mass in rats. NO-1886 also decreased plasma TG concentration and caused a concomitant rise in plasma HDL-C. Long-term administration of NO-1886 to rats and rabbits with experimental atherosclerosis inhibited the development of atherosclerotic lesions in coronary arteries and aortas. Multiple regression analysis suggested that the increase in plasma HDL-C and the decrease in plasma TG protect from atherosclerosis. The atherogenic lipid profile is changed to an antiatherogenic profile by increasing LPL activity, resulting in protection from atherosclerosis. Therefore, the LPL activator NO-1886 or other possible LPL activating agents are potentially beneficial for the treatment of hypertriglyceridemia, hypo-HDL cholesterolemia, and protection from atherosclerosis.