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Correspondence

Atorvastatin Increases Lipoprotein Lipase Expression *in vitro* and Activity *in vivo*

To the Editor:

Recently, Saiki *et al.* (1) reported an enhanced Lipoprotein Lipase (LPL)-activity and expression in pre-adipocytes mediated by pitavastatin treatment.

They state initially that the mechanism by which statins reduce triglycerides is thought to be due to the reduced VLDL-secretion from the liver (2), whereas little data about the catabolism of lipoproteins was available.

In fact, therapy with statins is associated with a decrease in triglycerides, but the mechanisms by which statins lower triglyceride levels are not exactly known. This effect and the particular benefit of a statin therapy for diabetic patients suggest an involvement of LPL.

In addition to pitavastatin, various other statins (pravastatin, simvastatin, atorvastatin) were tested by Saiki *et al.* (1) for their ability to increase LPL-activity *in vitro*, but surprisingly only simvastatin and pitavastatin (– 30%) increased LPL-activity. Pitavastatin treatment also resulted in a 42%-increase of LPL-protein and a 26%-increase in LPL-message. Finally, pioglitazone added to the culture media increased LPL-activity with an additional increase of LPL-activity when pitavastatin was added that, in turn, could be prevented by pre-incubation with mevalonate.

The authors concluded from their study that the increased LPL-activity by pitavastatin treatment *in vitro* may not be mediated by a PPARγ-dependent mechanism, and that this pitavastatin-driven effect may be different from the triglyceride lowering effect of other statins.

The conclusions made in this detailed study do partly complement the observations made in previous studies. However, we think that the statin effect on LPL is not restricted to pitavastatin or simvastatin. It has been shown that atorvastatin is able to induce LPL gene expression in 3T3-L1 pre-adipocytes (3). Moreover, atorvastatin and pravastatin elevated pre-heparin lipoprotein lipase mass of type 2 diabetics with hypercholesterolemia (4), although the measurement of pre-heparin LPL-activity is of uncertain significance. Our own study revealed a 25%-increase of LPL-activity in type 2 diabetic patients by atorvastatin (5). We obtained similar results when evaluating the effect of pravastatin (Schneider J.G. *et al.*, unpublished). In rabbits, statin treatment resulted in a 72% increase in LPL activity (6). Interestingly, for pitavastatin, no LPL-mediated effect on triglycerides has been found in an animal model of postprandial lipemia (7).

Regarding the mechanism by which statins induce increased LPL-activity, the *in-vitro* data obtained by Saiki *et al.* (1) suggest a direct effect on LPL-transcription. Accordingly, we did not obtain evidence for a potential indirect mechanism consisting of an atorvastatin-mediated change in the plasma ratio of the LPL-activitating apo C-II to the LPL-inhibiting apo C-III (5). Conversely, the recent finding of a functional responsive element for sterol regulatory binding proteins (SREBP) (8) in the LPL promoter supports the hypothesis of an increased LPL promoter activity mediated by cholesterol depletion of the cell.

Especially patients with type 2 diabetes mellitus that have a particular high risk for coronary artery disease have shown to benefit from lipid lowering therapy with statins (9), although the typical lipid profile of diabetic patients is characterized by elevated triglycerides and low HDL-cholesterol, rather than elevated LDL- cholesterol. Lower plasma LPL-activity has not only been found in diabetes and insulin resistance but is also considered to be pro-atherogenic. The finding of a statin-mediated increase in LPL-activity could help to explain the reduction of cardiovascular morbidity and mortality in statin trials in both, diabetic and non-diabetic patients.

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Jochen G. Schneider
Maximilian v. Eynatten
Klaus A. Dugi
Department of Internal Medicine I (Endocrinology and Metabolism) University of Heidelberg