Karolinska Institutet

Institutionen för Laboratoriemedicin

Avdelningen för klinisk farmakologi

Pleiotropic Effects of HMG-CoA Reductase Inhibitors

- studies *in vitro* and *in vivo*

AKADEMISK AVHANDLING
som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i sal 9Q Månen, Alfred Nobels Allé 8, Karolinska Universitetssjukhuset Huddinge.

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Abstract

Cardiovascular disease (CVD) is the prime cause of death in industrialized countries, resulting from the progression of atherosclerotic lesions. An increased level of plasma cholesterol, particularly within low-density lipoproteins, is a principle risk factor, but also elevated triglycerides and low levels of high-density lipoprotein cholesterol. Recognition of dyslipidemia as a risk factor for CVD has led to an international consensus that anti-hyperlipidemic drug therapy is essential for the primary and secondary prevention in risk patients. HMG-CoA reductase inhibitors, i.e. statins, are the most common drugs used for this purpose, inhibiting the rate-limiting step in cholesterol biosynthesis. The medical significance of HMG-CoA reductase inhibitors have in recent years been expanded to include cholesterol-independent or "pleiotropic" vascular effects, including improvement of vascular endothelial function, inhibition of vascular smooth muscle cell proliferation and migration, anti-inflammatory actions, anti-oxidative effects or stabilization of vulnerable plaques. These effects have potential in the treatment of coronary artery disease in various settings, such as prevention of its onset as well as its progression. The major aim of this thesis was to contribute to the general knowledge about the pleiotropic effects of statins, particularly in relation to the vascular endothelium and to carcinogenesis.

We found that fluvastatin at clinically relevant doses up-regulates transcription and translation of prostacyclin synthase and endothelial nitric oxide synthase in human vascular endothelial cells, associated with an increase in cellular production of prostacyclin (PGI_2) and nitric oxide (NO), and induces rapid dilatation in isolated human arteries via contribution of endothelium derived factors like NO and PGI_2. These results suggest beneficial effects of fluvastatin on endothelial maintenance *in vivo* and a protective role on the cardiovascular system, particularly at the level of vascular endothelium. We also show that simvastatin induces a potentially negative alteration of vascular endothelial cells both *in vivo* and *in vitro*. Exposure of clinically comparable concentrations of simvastatin led to decreased production and release of PGI_2 in endothelial cells and to significantly increased urinary thromboxane A_2 (TXA_2) levels in healthy volunteers, possibly resulting in a shift of the balance between PGI_2 and TXA_2, favoring the thromboxane pathway. Fluvastatin and simvastatin were also shown to have different impact on vascular endothelial oxidative stress status, both in cultivated endothelial cells and in healthy volunteers. Compared to simvastatin, fluvastatin seems beneficial both regarding expression of anti-oxidative stress enzymes and reactive oxygen species activity *in vitro* and anti-oxidative capacity *in vivo*. The suggested anti-carcinogenic properties of statins in relation to expression of the redox-active enzymes thioredoxin reductases (TrxR) were investigated in paper IV. We found that statin treatment decreases the hepatic expression of TrxR1 in humans and rats. In addition, the decreased TrxR1-levels were correlated with inhibited carcinogenesis in rat liver. The effect on TrxR1 levels might explain some of the anti-carcinogenic effects of statins.

Overall, our results add to the conjecture that the impact on production of vascular active substances may be significantly different among the statins, and thus the consequences of statin exposure may not be drug class related but rather compound specific, highlighting the importance of more comparative studies where several statins are included. These findings add novel insight in the field of pleiotropic effects of statins and provide some insight for functional differences among statins.

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