Statins Induce the Gene Expression of Apolipoprotein A5 in HepG2 Cells

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Abstract: The apolipoprotein A5 (apoA5) is fast gaining attention as a key regulator of plasma triglyceride concentrations. Statins are drugs that improve cholesterol levels primarily by inhibiting the rate-limiting enzyme in cholesterol synthesis. They also have a moderate ability to reduce plasma triglyceride levels. We investigated the ability of pitavastatin and pravastatin to modulate gene expression and synthesis of apoA5 in HepG2 cells. Promoter activity of the *APOA5* gene was estimated by measuring luciferase activity of plasmids with an *APOA5* promoter region transfected into human hepatoma HepG2 cells. Total RNA of HepG2 cells was extracted and analyzed by real-time quantitative PCR using *APOA5*-specific oligonucleotides. ApoA5 concentrations were measured by the ELISA. Exposure of HepG2 cells to 1–30 μM pitavastatin or 10–50 μM pravastatin resulted in significant increases in luciferase activity, and cotransfection of a peroxisome proliferator-activated receptor (PPAR) α resulted in an additional increase in *APOA5* gene expression. These effects were reversed by the addition of mevalonate or geranylgeranyl pyrophosphate, implicating HMG-CoA reductase as the relevant target of these drugs. HepG2 cells treated with pitavastatin displayed a strong induction of *APOA5* mRNA, and 5 μM pitavastatin increased the concentration of apoA5 in culture medium of HepG2 cells. Our results demonstrate that the gene expression and synthesis of apoA5 in HepG2 cells is regulated by statins in a positive manner, through suppressing the synthesis of mevalonate or its downstream products.

Key words: **Apolipoprotein A5, HepG2, luciferase activity, Pitavastatin, Statin**