

Nutritional status affects fluvastatin-induced hepatotoxicity and myopathy in rats: Association with the suppression of hepatic organic anion transporting polypeptide 2

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3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins), whose competitive inhibition of HMG-CoA reductase reduces the amount of HMG-CoA converted to mevalonate, the rate-limiting step of cholesterol biosynthesis, are members of an important class of lipid lowering drugs. While statins appear to be relatively safe and well tolerated, considerable attention has recently been paid to their adverse effects including muscular toxicity and hepatotoxicity. These side effects are a major concern in that they can lead to severe myopathy, rhabdomyolysis, renal damage, and even death.

Rats that consumed a high-fat and high-sucrose (HF) diet developed hepatic steatosis. Treatment with fluvastatin (8 mg/kg) ameliorated hypertriglycemia and hepatic steatosis in rats on a standard (SD) diet, but caused an elevation in levels of plasma aspartate aminotransferase (AST) and creatine kinase activities, leg muscle weakness and myositis in those on the HF diet. Fluvastatin at the concentration detected in the plasma of HF diet-fed rats caused the release of AST from Chang liver cells and suppression of cell growth. Thus, this study was conducted to determine whether the increase in systemic exposure resulted from suppression of the uptake or metabolism of fluvastatin in liver. No significant difference in the baseline level of the Oatp1, Oatp2, Mrp2, Mrp3, Mdr1b, CYP1A, CYP2C, CYP3A, UGT1A5, or UGT2B1 protein was found between the SD and HF diet-fed groups. In contrast, Oatp1, Mrp3, CYP1A, CYP2C, and UGT2B1 protein levels were moderately decreased and CYP3A and Oatp2 mRNA and protein levels were markedly suppressed by fluvastatin, while Mrp2, Mdr1b, UGT1A1, and UGT1A5 protein levels were not significantly changed. In liver cell nuclei, levels of constitutive androstane receptor, pregnane X receptor, and hepatocyte nuclear factor 4a proteins were decreased in fluvastatin-treated HF diet-fed rats, which correlated with the decrease in Oatp2, CYP2C, and CYP3A. Taken together, these results indicate that nutritional status may influence the adverse effects of fluvastatin, and inhibition of transporter-mediated hepatic uptake in the HF diet-fed group may have resulted in suppression of fluvastatin's elimination. Preceding to elevation in serum CK levels and muscle damage, serum AST levels were elevated in HF diet-fed rats by fluvastatin treatment. In order to prevent severe adverse effects in patients carrying hepatic steatosis, we should be careful in elevation in serum AST levels as the sign, although whether AST elevation with statin therapy constitutes true hepatotoxicity has not been determined