In Vivo and *in Vitro* Studies on the Regulatory Link between 3-Hydroxy-3-methylglutaryl Coenzyme A Reductase and Cholesterol 7α-Hydroxylase in Rat Liver

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The activities of 3-hydroxy-3-methylglutaryl CoA reductase (HMGCoA reductase; EC 1.1.1.34), rate-limiting enzyme of cholesterol biosynthesis, and cholesterol 7α-hydroxylase (EC 1.14.13.17), key enzyme of the neutral bile acid synthesis pathway, were measured in the microsomal fraction of rat liver and in rat liver cells to investigate the coordinate regulation of the two pathways.

Both enzyme activities exhibited the same diurnal rhythm and responded in a coordinate fashion to fasting or bile acid-feeding (decrease) and to cholestyramine-feeding (increase). Cholesterol-feeding decreased the activity of HMGCoA reductase, increased that of cholesterol 7α-hydroxylase, and concomitantly increased free cholesterol in microsomes.

In an *ex vivo* setting using primary hepatocytes from animals fed a high cholesterol diet the activity of HMGCoA reductase was initially low and that of cholesterol 7α-hydroxylase was elevated. Release of cholesterol into the medium with ongoing incubation caused HMGCoA reductase activity to increase, and that of cholesterol 7α-hydroxylase to decline. Incubation of hepatocytes with a cholesterol-containing lipoprotein fraction stimulated the activity of cholesterol 7α-hydroxylase, but left HMGCoA reductase activity unaffected.

The results confirm the idea of a joint regulation of the two key enzymes of cholesterol metabolism in response to the levels of substrate and metabolites, and support the notion that with respect to bile acid and cholesterol levels, respectively, regulation of HMGCoA reductase activity may be secondary to that of cholesterol 7α-hydroxylase. The *in vitro* studies supply evidence that the effects of cholesterol and bile acid excess or deficiency are direct and do not involve accessory changes of hormone levels or mediators.

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