Inhibition of 3-hydroxy-3-methylglutaryl-CoA reductase activity and gene expression by dehydroepiandrosterone in preneoplastic liver nodules.


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Previous work has demonstrated that dehydroepiandrosterone (DHEA) strongly inhibits growth and de novo cholesterol (CH) biosynthesis in preneoplastic rat liver. Administration of a mixture of 4 ribo- or deoxyribonucleosides of adenine, guanine, cytosine and uracil/thymine, prevents growth inhibition but not inhibition of CH synthesis. The purpose of this paper was to identify the site of inhibition of CH synthesis by DHEA. Persistent nodules (PNs) were induced, in diethylnitrosamine-initiated male F344 rats, by 'resistant hepatocyte' protocol. Fifteen weeks after initiation, nodule bearing rats and normal controls received a diet containing 0.6% DHEA for 3 weeks. They were then killed. 3-Hydroxy-3-methylglutaryl-CoA reductase (HMGR) activity and mRNA levels were 18- and 14-fold higher, respectively in nodules than in normal liver. DHEA strongly inhibited HMGR activity in both tissues in vivo, but had a slight effect on HMGR activity, when added in vitro to the reaction mixture for determination of this activity. In vivo DHEA treatment caused a 65% decrease in the level of HMGR mRNA in PNs, which, however, does not seem to completely account for the decrease in HMGR activity (83%). Low density lipoprotein receptor (LDL-R) mRNA level underwent a slight decrease in PNs, with respect to control liver, which did not lead to a significant decrease in 125I-LDL binding to LDL-R. DHEA treatment caused 30% and 24% increases in LDL-R expression and 125I-LDL binding, respectively, in nodules. These observations indicate that in addition to HMGR gene expression, increased influx of LDL into preneoplastic cells may contribute to the deregulation of mevalonate synthesis by DHEA. The observation that HMGR activity and gene expression were still 3- to 5-fold higher in PNs of DHEA-treated rats than in control liver, and previous findings of preneoplastic liver cell growth in the presence of relatively low CH synthesis, suggest that even relatively low levels of mevalonate are sufficient for the growth of preneoplastic liver cells.

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