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Lovastatin decreases coenzyme Q levels in rats

(3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors/ubiquinone)

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ABSTRACT **Lovastatin is used for the treatment of hypercholesterolemia. It functions by inhibiting the enzyme, 3-hydroxy-3-methylglutaryl-coenzyme A reductase (EC 1.1.1.34), that is required for the conversion of 3-hydroxy-3-methylglutaryl-coenzyme A to mevalonic acid. Since biosynthesis of both cholesterol and coenzyme Q (CoQ) requires mevalonic acid as a precursor, it was considered that lovastatin therapy would also result in a lowering of cellular CoQ levels. This study was conducted to determine whether lovastatin treatment does decrease CoQ levels and whether such decreases can be prevented by CoQ supplementation. Forty-five adult male Holtzman rats were randomly assigned to one of three treatment groups. Controls were fed ground laboratory rat chow ad libitum. The other two groups were fed ground laboratory rat chow containing 400 mg of lovastatin per kg of diet ad libitum. One of the lovastatin-fed groups received CoQ_{10} (15 mg per kg of body weight) daily via stomach intubation. After 4 weeks, samples of heart, liver, and blood were analyzed for CoQ concentrations. Results indicated that CoQ concentrations in all tissues analyzed were decreased in lovastatin-treated rats. Lovastatin-treated animals that were supplemented with CoQ_{10} had blood, heart, and liver CoQ_{10} concentrations that approximated or exceeded those of control animals. It is concluded that lovastatin does indeed lower tissue concentrations of CoQ and that a return to normal can be achieved by supplementation with CoQ.**

Lovastatin is widely used for the clinical treatment of hypercholesterolemia. It functions by inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the enzyme required for the conversion of HMG-CoA to mevalonic acid. This step is intermediate in the multistep pathway for cholesterol biosynthesis from acetyl-CoA. The biosynthesis of cholesterol is thus inhibited, leading to a reduction of circulating cholesterol in patients (1). The biosynthesis of coenzyme Q (CoQ, also called ubiquinone) takes place by the formation of the quinone nucleus from tyrosine and formation of the side chain from mevalonic acid. It has been stated (2) that "Because Mevacor [lovastatin] does not inhibit HMG-CoA reductase completely, biologically necessary amounts of mevalonate are available." This statement implies that the residual "necessary amounts of mevalonate" are sufficient for the biosynthesis of CoQ. However, we considered that lovastatin therapy of diverse human subjects with elevated levels of cholesterol could also reduce cellular CoQ levels, which, in turn, could be detrimental to the health of such patients. For example, cardiac function and immune-system function could be depressed by decreased CoQ biosynthesis. Results of a clinical study showing reductions of CoQ_{10} levels by lovastatin therapy and reductions in cardiac function are presented in the accompanying report by Folkers *et al.* (3).

CoQ_{10} (the subscript indicates the number of isoprene units in the side chain) is an important participant in electron transport in the respiratory chain in mammalian mitochondria (2–9). Evidence has been accumulating over the last two decades that this coenzyme may be important in a variety of clinical conditions. Essential hypertension, periodontal disease, lichen planus, doxorubicin-induced cardiotoxicity, cardiac output in heart patients, renal ischemia survival, and hepatic damage by antineoplastic drugs (mitomycin C and 5-fluorouracil dry syrup) have been reported to improve or be mitigated by CoQ_{10} treatment (10–24). It is likely and very important that some, if not most, of the side effects associated with the use of lovastatin in treatment of hypercholesterolemia are due to a decrease in CoQ_{10} levels.

Known side effects of lovastatin include marked, persistent increases in serum transaminases, myalgia, myositis, increased creatine kinase levels, renal failure, and, in mice, tumors of liver, lung, and stomach (2). Therefore, it is plausible that many of the side effects associated with the use of lovastatin in treatment of hypercholesterolemia are due to a decrease in CoQ_{10} levels.

This study in the rat model was undertaken to determine whether lovastatin treatment does indeed decrease CoQ levels and whether such decreases can be prevented by CoQ supplementation.

METHODS

Forty-five adult male Holtzman rats were randomly assigned to one of three treatment groups (15 rats per group). Group I (controls) were fed ground laboratory rat chow (Purina) ad libitum. Groups II (lovastatin treatment group) and III (lovastatin plus CoQ treatment group) were fed ground laboratory rat chow containing 400 mg of lovastatin per kg of diet ad libitum. The lovastatin was purchased as 20-mg tablets from a retail pharmacy; the pills were ground and mixed with the rat chow. Group III received CoQ_{10} (15 mg/kg of body weight) daily via gastric intubation. Body weights were determined weekly and weight of food consumed was recorded daily. After 4 weeks, the animals were euthanized with carbon dioxide and samples of heart, liver, and blood were analyzed for CoQ_9 and CoQ_{10} concentrations (25). One-way analysis of variance and Scheffe multiple range tests were used for statistical analysis of all data.

RESULTS

Initial body weights were 480.2 ± 26.8 g, 471.4 ± 27.2 g, and 478.6 ± 23.0 g (mean ± SD, $n = 15$) for groups I, II, and III, respectively. Final mean body weights were 564.6 ± 40.3 g, 554.3 ± 30.8 g, and 517.1 ± 44.3 g for groups I, II, and III, respectively. The slight lowering of weight gain was expected in the intubated group. A previous pilot study with sham intubation of the non-CoQ-treated groups showed no differences between group weight gain. Mean daily food intakes

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Abbreviations: HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme A; CoQ, coenzyme Q.

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were 27.6 g, 28.5 g, and 23.1 g for groups I, II, and III, respectively.

Gross examination of the animals at the conclusion of the study revealed no obvious abnormalities of skin, hair, eyes, etc. However, during the collection of liver tissue samples for biochemical analyses, it was noted that the gross appearance of the livers of the lovastatin-treated rats was markedly different from that of the controls and from that of the lovastatin plus CoQ_{10}-treated rats, which were similar in appearance. The livers of the lovastatin-treated group were lighter in color and mottled as compared to the livers of the other two groups.

CoQ_9 concentrations in blood, heart, and liver samples are displayed for each of the three groups in Fig. 1. Blood CoQ_9 concentrations were significantly ($P < 0.01$) decreased in the lovastatin (0.36 ± 0.07 μg/ml) and lovastatin plus CoQ_{10} (0.35 ± 0.08 μg/ml) treatment groups as compared to controls (0.54 ± 0.14 μg/ml). CoQ_9 concentrations in heart tissue were decreased in the lovastatin (1.11 ± 0.11 μg/mg) and lovastatin plus CoQ_{10} (1.15 ± 0.16 μg/mg) treatment groups as compared to controls (1.20 ± 0.11 μg/mg). While these differences were not statistically significant, they were in the predicted direction. CoQ_9 concentrations in liver tissue were significantly ($P < 0.01$) decreased in the lovastatin treatment group (0.21 ± 0.05 μg/mg) as compared to the lovastatin plus CoQ_{10} treatment group (0.33 ± 0.09 μg/mg) and the controls (0.30 ± 0.08 μg/mg).

Data on CoQ_{10} concentrations in blood, heart, and liver are displayed in Fig. 2. CoQ_{10} concentrations in blood were significantly ($P < 0.01$) increased in the lovastatin plus CoQ_{10} treatment group (0.41 ± 0.15 μg/ml) as compared to the control group (0.18 ± 0.05 μg/ml) and the lovastatin treatment group (0.13 ± 0.03 μg/ml). While the difference between the latter two groups was not statistically significant, it was in the predicted direction. CoQ_{10} concentrations in heart tissue were significantly ($P < 0.01$) decreased in the lovastatin treatment group (0.105 ± 0.01 μg/mg) as compared to the control group (0.122 ± 0.01 μg/mg) and the lovastatin plus CoQ_{10} treatment group (0.113 ± 0.02 μg/mg). CoQ_{10} levels in liver tissue were significantly ($P < 0.01$) increased in the lovastatin plus CoQ_{10} treatment group (0.46 ± 0.16 μg/mg) as compared to the control group (0.06 ± 0.04 μg/mg) and the lovastatin treatment group (0.05 ± 0.02 μg/mg). Again, while the difference between the latter two groups was not statistically significant, the difference was in the predicted direction.

DISCUSSION

In all instances (blood, heart, and liver) lovastatin treatment resulted in a decrease in CoQ concentrations. Supplementation with CoQ_{10} brought CoQ_{10} concentrations back to or above control levels. Considering the widespread use of lovastatin in human hypercholesterolemic patients, these findings are clinically significant. Since CoQ_{10} is essential for normal mitochondrial bioenergetics, any therapy that inhibits CoQ_{10} biosynthesis can produce a multitude of undesirable effects on the patient. In the accompanying report by Folkers *et al.* (3), the potential effect on cardiac function in human subjects is examined.

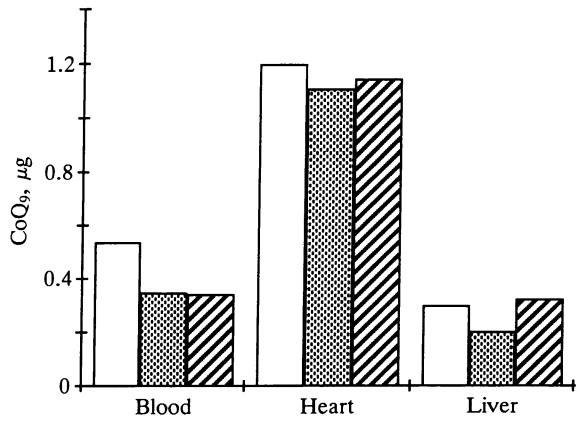

FIG. 1. CoQ_9 concentrations in rats. Open bars, control; stippled bars, lovastatin-treated; hatched bars, lovastatin plus CoQ_{10}-treated.

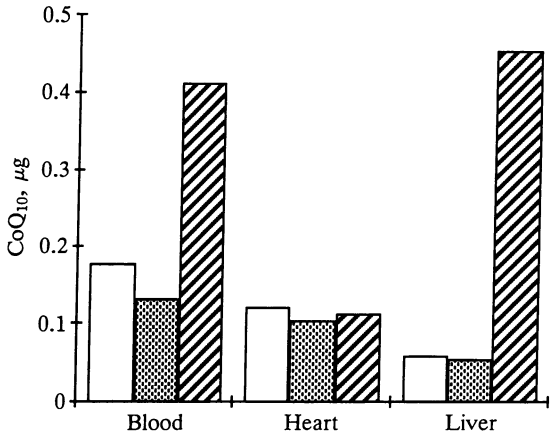

FIG. 2. CoQ_{10} concentrations in rats. Open bars, control; stippled bars, lovastatin-treated; hatched bars, lovastatin plus CoQ_{10}-treated.

The rat data reported here imply potential effects in all bioenergetically active tissues. When the reported side effects of lovastatin—marked persistent increases in serum transaminases, myalgia, myositis, increased creatine kinase levels, renal failure, and, in mice, tumors of liver, lung, and stomach—are considered in light of this demonstrated inhibition of CoQ synthesis, a possible explanation of the mechanism for production of many of these side effects appears.

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