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Note

Dietary Coenzyme Q10 Suppressed Hepatic Hydroxymethylglutaryl-CoA Reductase Activity in Laying Hens

Kazuhisa HONDA,† Takaoki SANEYASU, Tohru MOTOKI, Yuriko PARK, and Hiroshi KAMISOYAMA

Department of Bioresource Science, Graduate School of Agricultural Science, Kobe University, Kobe 657-8501, Japan

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The effects of dietary coenzyme Q10 (CoQ10) on cholesterol metabolism in laying hens were investigated. Dietary CoQ10 significantly reduced egg yolk cholesterol content and suppressed hepatic hydroxymethylglutaryl-CoA reductase (HMGR) activity. It is therefore likely that CoQ10 acts as an HMGR inhibitor in the livers of laying hens, which in turn results in a reduction in egg-yolk cholesterol.

Key words: coenzyme Q10; ubiquinone; egg yolk; cholesterol

Coenzyme Q (CoQ) is a naturally occurring compound with a ubiquitous distribution in nature. Based on an isoprenoid moiety, the presence of various CoQ homologs has been confirmed.[1,2] CoQ10, which has a polyisoprene chain containing 10 isoprene units, is predominant in humans and birds, whereas CoQ9 is predominant in rats and mice.[1,2] Two major functions are attributed to this compound: it acts as an electron carrier in the mitochondrial respiratory chain and as a lipid-soluble antioxidant.[3]

In humans, the amount of CoQ10 decreases rapidly after the age of 40.[4] Hence, CoQ10 is used as a dietary supplement to combat aging worldwide, and it has become increasingly popular. In chickens, dietary CoQ10 supplementation reduced broiler chickens' susceptibility to ascites, perhaps as a result of improved hepatic mitochondrial function, respiratory chain-related enzyme activities, and the mitochondrial antioxidative activity of CoQ10.[5] Recently, we found that dietary CoQ10 significantly reduced the levels of cholesterol in the egg yolks of laying hens,[6] but the mechanisms underlying this reduction in egg-yolk cholesterol have not been identified.

In mammals, a cholesterol-lowering effect of dietary CoQ has been reported. For example, dietary CoQ10 reduced the plasma total cholesterol concentration in diabetic rats.[7] CoQ9 suppressed hepatic cholesterogenesis and reduced serum cholesterol concentrations in rats.[8] Recently, we found that dietary CoQ10 significantly suppressed the enzymatic activity of hepatic hydroxymethylglutaryl-coenzyme A reductase (HMGR), the rate-limiting enzyme in the cholesterol synthetic pathway, in chicks.[9] In laying hens, cholesterol is biosynthesized primarily in the liver and is incorporated into VLDL, which is secreted into the bloodstream and subsequently taken up by growing oocytes, constituting about 95% of yolk cholesterol.[10] This VLDL particle, which has been termed yolk-targeted VLDL (VLDLy), contains large amounts of apoVLDL II. Since apoVLDL II is an inhibitor of lipoprotein lipase, most VLDLy particles escape lipolysis, ensuring efficient delivery of cholesterol to the growing oocytes. These findings led us to the hypothesis that dietary CoQ10 suppresses cholesterol synthesis in the liver, which in turn reduces egg yolk cholesterol in laying hens.

In the present study, we investigated the effects of CoQ10 on HMGR activity in laying hens.

Twenty 30-week-old Boris Brown hens were housed in wired laying cages (one bird per cage) and fed a commercial feed (91.2% solid, 18.5% crude protein, 5.2% crude fat, 12.3% ash; Nippon Formula Feed, Kanagawa, Japan) for 1 week before the experiment. The birds were assigned to two groups based on egg production rate and egg weight (eight birds in each group). In this experiment, pair-feeding was employed to keep the food and CoQ10 (CoQ10 99.5%; Kaneka, Osaka, Japan) intakes the same. The birds were pair fed at 100 g/d of commercial feed containing either 0 (as control) or 0.8% CoQ10 for 28 d. Eggs were collected every day at 12 AM and weighed. The weights of the egg shells and egg yolks and the concentrations of egg yolk cholesterol were measured at 7, 14, 21, and 28 d. At the end of the experiment, the hens were sacrificed by decapitation and blood was collected. Plasma was separated and plasma total, LDL, and VLDL-cholesterol was analyzed as described previously.[9] The liver was excised and weighed, and total cholesterol, microsomal HMGR activity, and hepatic HMGR mRNA levels were analyzed as described previously.[9] All experimental procedures followed the Guidelines for the Care and Use of Experimental Animals of the Rokkodai Campus of Kobe University. All data were analyzed by Student's t test.

The egg-yolk cholesterol level was significantly lower after week 3 (Table 1). The plasma VLDL-cholesterol concentration was tended to decrease due to dietary CoQ10 ($p < 0.072$) (Table 2). Hepatic HMGR activity in the CoQ10 group was significantly lower than in the control group (Table 2).

In the present study, we did not measure the CoQ10 levels of the experimental feeds, but corn and soybean, which were major feed ingredients in the experimental feed, contain 0% and 0.00068–0.0019% CoQ10 respectively.[11] Furthermore, the CoQ10 levels in most food

† To whom correspondence should be addressed. Fax: +81-78-803-5809; E-mail: honda@tiger.kobe-u.ac.jp
Abbreviations: CoQ10, coenzyme Q10; HMGR, hydroxymethylglutaryl-coenzyme A reductase; VLDL, very low density lipoprotein

Table 1. Effects of Coenzyme Q10 on Egg Weight, Egg Yolk Weight, Egg Shell Weight, Egg Production, and Egg-Yolk Cholesterol in Laying Hens

	Treatment	Week 1	Week 2	Week 3	Week 4
Egg weight (g)	Control	63.30 ± 1.97	62.04 ± 2.95	63.66 ± 2.62	63.66 ± 2.95
	CoQ10	59.82 ± 0.81	58.79 ± 1.25	58.87 ± 1.80	61.31 ± 1.87
Egg yolk weight (g)	Control	14.21 ± 0.23	13.90 ± 0.33	14.12 ± 0.28	14.24 ± 0.47
	CoQ10	14.07 ± 0.38	13.64 ± 0.39	13.76 ± 0.63	14.08 ± 0.52
Egg shell weight (g)	Control	5.92 ± 0.34	6.44 ± 0.23	6.41 ± 0.31	6.30 ± 0.23
	CoQ10	6.06 ± 0.19	6.06 ± 0.13	5.90 ± 0.23	6.21 ± 0.15
Egg production rate (%)	Control	73.81 ± 5.73	73.81 ± 2.38	76.19 ± 4.76	66.67 ± 3.01
	CoQ10	81.63 ± 4.08	79.59 ± 2.89	81.63 ± 2.63	73.47 ± 3.73
Egg yolk cholesterol content (mg/yolk)	Control	198.63 ± 3.45	194.11 ± 5.47	196.75 ± 5.75	201.65 ± 9.51
	CoQ10	185.28 ± 5.64	184.27 ± 9.35	170.59 ± 7.98*	175.62 ± 6.55*

Values were means ± SEM for eight birds in each group. *Significant with respect to control group ($p < 0.05$).

Table 2. Effects of Coenzyme Q10 on Cholesterol Methabolism in Laying Hens

	Control	Coenzyme Q10
Body weight (kg)	1.78 ± 0.07	1.83 ± 0.03
Liver weight (g)	35.24 ± 1.53	35.19 ± 2.00
Feed intake (g/d)	98.09 ± 0.30	96.73 ± 0.28
Plasma		
Total cholesterol (mg/100 mL)	57.63 ± 5.63	51.42 ± 4.08
LDL-cholesterol (mg/100 mL)	8.85 ± 1.22	8.45 ± 1.08
VLDL-cholesterol (mg/100 mL)	40.39 ± 5.02	32.57 ± 3.41
Liver		
Cholesterol (mg/g)	3.53 ± 0.15	3.67 ± 0.07
HMGR activity (pmol/min/mg protein)	7.19 ± 0.75	3.50 ± 0.71*
HMGR mRNA (Arbitrary unit)	1.91 ± 0.72	1.12 ± 0.22

Values were means ± SEM for eight birds in each group.
*Significant with respect to control group ($p < 0.01$).

are also very low (<0.005% class) as compared with the dose we used in this study (0.8%). We have found that CoQ10 levels in the liver and plasma increased more than 5-fold with the addition of 0.8% CoQ10 in a commercial diet in laying hens.[6] These findings and our present results suggest that the significant changes in hepatic HMGR activity and egg-yolk cholesterol levels were due to the addition of CoQ10 to the feed.

From a nutritional standpoint, eggs are an excellent source of high-quality protein, mono- and poly-unsaturated fatty acids, several minerals, and numerous fat- and water-soluble vitamins.[12] However, it is recommended that people limit their consumption of eggs due to their high cholesterol content.[13] For example, Nakamura *et al.* indicated that limiting egg consumption may have some health benefits, at least for women in geographic areas where egg consumption makes a relatively large contribution to total dietary cholesterol intake.[14] Therefore, research efforts directed toward reducing egg cholesterol content have centered on altering the diet of laying hens with various pharmacological agents and natural products.[10] In the present study, we found that the natural product CoQ10 significantly reduced the content of cholesterol in egg yolks (Table 1). In addition, we have found that dietary CoQ10 significantly increased the levels of CoQ10 in the egg yolks, from 4.35 ± 0.44 μg/g to 22.46 ± 2.00 μg/g.[6] These findings indicate that dietary CoQ10 improves the quality of eggs in laying hens.

The enzymatic activity of HMGR in the liver was decreased by dietary CoQ10, whereas the mRNA level of HMGR was not affected (Table 2). It is therefore possible that dietary CoQ10 suppresses HMGR at the post-transcriptional levels. In rats, dietary CoQ9 suppresses hepatic cholesterogenesis.[8] The linker domain of HMGR, which is associated with inactivation of the enzyme,[15] is perhaps involved in the suppression of enzymatic activity by dietary CoQ9 in rats.[16] CoQ10 ingestion leads to an increase in tissue CoQ9 in rats and mice.[17] Whether such a conversion occurs in chickens is not clear at this time, but we have found that dietary CoQ10 significantly increased hepatic CoQ10 levels in laying hens.[6] We found recently that the addition of CoQ10 to the medium of chicken hepatoma cells suppressed HMGR activity (unpublished data). Thus, it is likely that CoQ10 or its metabolites directly inhibit HMGR activity in the liver of laying hens. Further study is needed to clarify the molecular mechanism underlying the suppression of HMGR activity by CoQ10.

Cholesterol intake from a conventional laying diet is minimal, requiring the hen to synthesize most of the large amount of cholesterol needed for the egg.[18] It is thus reasonable to assume that suppression of hepatic cholesterol synthesis lowers the cholesterol levels of the egg yolk in laying hens. In fact, several HMGR inhibitors, which suppress cholesterol biosynthesis in the liver,[11] reduce egg-yolk cholesterol in laying hens.[10] In the present study, dietary CoQ10 suppressed HMGR activity and reduced egg-yolk cholesterol in them. Thus it is likely that dietary CoQ10 suppresses cholesterol synthesis in the liver, and that this in turn reduces egg yolk cholesterol in laying hens.

In the present study, hepatic cholesterol and plasma LDL-cholesterol levels were not affected by CoQ10, although hepatic HMGR activity was significantly decreased. In laying hens, the kidney also produces VLDL particles, which are metabolized to LDL particles.[10] Hence the plasma LDL-cholesterol level is affected not only by hepatic VLDL production but also by renal VLDL production. Also, the hepatic cholesterol level was maintained by suppression of VLDL production, promotion of LDL uptake from the circulation through the receptor-mediated pathway, and/or suppression of the cholesterol catabolic pathway. In contrast, egg-yolk cholesterol was primarily affected by hepatic VLDL production.[10] It is thus possible that only the egg-yolk cholesterol level was significantly decreased by CoQ10. Further study is required to test this possibility.

There is evidence that egg-yolk cholesterol levels can be reduced by up to 46% following oral administration to

laying hens of atorvastatin, a drug for hyperlipidemia,[10] but dietary atorvastatin is possibly transferred into the egg yolk in laying hens.[19] CoQ10 was also transferred into the egg yolk, but it is a naturally occurring compound used as a dietary supplement to combat aging worldwide. Thus CoQ10 might be used to a functional feed additive, although the cholesterol-lowering effect of CoQ10 is weaker than that of atorvastatin.

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