The Protection of Coenzyme Q₁₀ against Experimental Viral Myocarditis in Mice

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We studied the effects of Coenzyme Q₁₀ (CoQ₁₀) on DBA/2 mice inoculated with the M variant of encephalomyocarditis virus. The mice were treated as follows: 1) CoQ group (n = 49); CoQ₁₀ 1.0 mg (0.1 ml) × 2/day (0.1 mg/g/day), 2) control group (n = 55); sham-liquid 0.1 ml × 2/day. These treatments were intraperitoneally performed every day on days -1 to 12. In both groups, we determined the heart and serum contents of CoQ₉ and CoQ₁₀, which are the biologically active forms of CoQ in mice, in the mice killed on days 3-4 and 7. There was no significant change in the cumulative incidence of myocarditis in both groups. The survival rate was significantly higher on days 5-12 in the CoQ group than in the control group. There were significant increases of CoQ₉ content on days 3-4, and CoQ₁₀ content on days 3-4 and 7, in the heart in the CoQ group as compared with the control group. There was no significant change in the serum content of CoQ₉ in both groups. The marked increase of the serum CoQ₁₀ content seen in the CoQ group was due to the results of the exogenous administration of CoQ₁₀. Thus, it may be concluded that CoQ₁₀ may have a protective effect against viral myocarditis in man, in whom CoQ₁₀ is only an active form of CoQ.

MYOCARDITIS is an inflammatory disease of the myocardium caused by viruses, bacteria and other cardiotoxic agents.¹⁻² Cardiac lesions of myocarditis include inflammatory cell infiltrations, myocardial cell necrosis and residual myocardial fibrosis.¹⁻⁶ However, the initial phenomenon occurring in the myocardium of myocarditis is considered to be myocardial ischemia.

Ubiquinones (coenzymes Q = CoQ) have long been known to be constituents of mitochondria and their role as electron and proton carriers in

respiration has been noted.⁷ In some clinical and experimental studies, CoQ₁₀ has protective effects against adriamycin induced myocardial damage and myocardial ischemia.⁸⁻¹⁰

The purpose of this study was to establish whether CoQ₁₀ could have a protective effect against viral myocarditis in mice.

METHODS

Our methods were similar to those reported previously^{5,6}: inbred strain of DBA/2 mice at 4-6 weeks of age were inoculated intraperitoneally with the M variant of encephalomyocarditis (EMC) virus with a titer of 100 TCID₅₀ per 0.1 ml and were observed up to the 12th day. The mice were divided and treated as follows: 1) CoQ group (n = 49); CoQ₁₀ 1.0 mg (0.1 ml) ×

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Fig. 1. Survival rate in both groups.
CoQ = CoQ group; Control = control group
Survival rate was significantly higher on days 5–12 in the CoQ group than in the control group.

Fig. 2. Changes in the heart content of CoQ₉.
Cont. = control group

Fig. 3. Changes in the heart content of CoQ₁₀.

Fig. 4. Changes in the serum contents of CoQ₉ and CoQ₁₀.

2/day (0.1 mg/g/day), 2) control group (n = 55); sham-liquid 0.1 ml × 2/day. These treatments were intraperitoneally performed every day on days –1 to 12. Their hearts were fixed in a 10% formalin solution, sectioned longitudinally through the four chambers.

In both groups, we determined the heart and serum contents of CoQ₉ and CoQ₁₀, which are the biologically active forms of CoQ in mice, in the mice killed on days 3–4 and 7, using the high performance liquid chromatography method.¹¹ We also determined the heart and serum contents of CoQ₉ and CoQ₁₀ in normal DBA/2 mice at 4–6 weeks old.

RESULTS

There were no significant changes in the cumulative incidence of myocarditis in both

groups; CoQ group = 85.7% (42/49), control group = 92.7% (51/55). However, the survival rate was significantly higher on days 5–12 in the CoQ group than in the control group (Fig. 1: 12th day; CoQ group = 45.5% (15/33), control group = 17.5% (7/40)). Table I shows normal heart and serum contents of CoQ₉ and CoQ₁₀ in the mouse.

There was a significant increase ($p < 0.05$) in the heart content of CoQ₉ on days 3–4 in the CoQ group ($237.5 \pm 15.3 \mu\text{g/g}$, $n = 8$) as compared with the control group ($213.9 \pm 25.5 \mu\text{g/g}$, $n = 10$) (Fig. 2). There was no significant change in the heart content of CoQ₉ on day 7 in both groups (CoQ group = 204.7 ± 24.7 , $n = 8$, control group = 215.3 ± 33.5 , $n = 5$) (Fig. 2).

There were significant increases ($p < 0.001$) in the heart content of CoQ₁₀ on days 3–4 and on day 7 in the CoQ group (3–4 day; 95.0 ± 26.9

(a)

(b)

Fig. 5. Light microscopical pictures of the left ventricle in both groups.
((a) = CoQ group, (b) = control group).
Note the presence of massive myocardial necrosis with calcification in the control group. HE $\times 370$ (a, b)

$\mu\text{g/g}$, $n = 8$, 7th day; 76.5 ± 20.0 , $n = 8$) as compared with the control group (3–4 day; 20.4 ± 2.0 , $n = 10$, 7th day; 24.4 ± 2.8 , $n = 5$) (Fig. 3).

Concerning the serum contents of CoQ₉ and CoQ₁₀, there was no significant change of the CoQ₉ content in both groups (CoQ group = $0.42 \pm 0.12 \mu\text{g/ml}$, $n = 10$; control group = 0.49 ± 0.14 , $n = 6$), but a marked increase of the CoQ₁₀ content in the CoQ group ($20.5 \pm 13.2 \mu\text{g/ml}$, $n = 12$) was observed as compared with the control group (not detected, $n = 10$) (Fig. 4). However, this phenomenon with a marked high value of the serum CoQ₁₀ content seen in the CoQ group was due to the results of the exogenous administration of CoQ₁₀.

The pathologic study demonstrated that there were no particular changes in the myocardial lesions of myocarditis in both groups. However, the CoQ group had a lower severity tendency of myocarditis (Figs. 5 (a), (b)).

TABLE I NORMAL VALUES OF CoQ₉ AND CoQ₁₀ DETERMINED FROM NORMAL DBA/2 MICE AT 4–6 WEEKS OF AGE

Sample	Co-Q Concentrations in Mouse ($\mu\text{g/g}$ or ml)	
	Co-Q ₉	Co-Q ₁₀
Heart	317.7 ± 29.5 ($n = 15$)	32.7 ± 3.9 ($n = 15$)
Serum	0.32 ± 0.09 ($n = 8$)	---- ($n = 12$)

---- = not detected.

DISCUSSION

Coenzyme Q₁₀ is a physiologically essential substance in man as one of the respiratory chain members in mitochondria, and has been known to exist abundantly in the heart, which repeats the contraction and relaxation cycle continuously. CoQ₁₀ deficiency in ischemic heart tissue and the amelioration of cardiac function by CoQ₁₀ replenishment have been previously demonstrated^{8–10}

In this experimental study, we found a significantly higher survival rate in the CoQ group as compared with the control group. We also found higher contents of CoQ₉ and CoQ₁₀ in the myocardium of the CoQ group as compared with the control group. In addition, the values of CoQ₉ and CoQ₁₀ contents in the hearts of the mice with myocarditis were demonstrated to be lower than those of the normal mice (Table I and Figs. 2, 3). Thus, CoQ₉ and CoQ₁₀ may play some role against viral myocarditis in mice.

Although further studies may be necessary to determine the precise mechanism of CoQ₁₀ against viral myocarditis in mice, it may be suggested that CoQ₁₀ could have a protective effect against viral myocarditis in man, in whom CoQ₁₀ is only an active form of CoQ¹¹

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