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Effect of Dietary Coenzyme Q_{10} on Lipid Peroxidation in Adriamycin-treated Rats

— I. Effect on Lipid Peroxide Metabolizing Enzyme Activities —

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ABSTRACT

This present study was designed to evaluate whether supplementaion of dietary coenzyme Q_{10} protects the lipid peroxidation damage in adriamycin (ADR)-treated rats. Two experiments were conducted in this study. Experiment I was undertaken under the condition of simultaneous administration of ADR and coenzyme Q_{10} for 4 weeks. Experiment 2 was undertaken under the same condition as experiment I after feeding the experimetal diets alone without administration of ADR for 4 weeks.

Results obtained from the present study were as follows. Lipid peroxide value of plasma and heart mitochondria was elevated by ADR treatment, but decreased according to dietary coenzyme Q_{10} supplementation. Pretreatment with dietary coenzyme Q_{10} was more efficient in reducing ADR-induced lipid peroxide value. The simultaneous use of ADR and coenzyme Q_{10} enhanced the heart glutathione peroxidase(GSH-Px) activity, particularly at higher level of coenzyme Q_{10}. The change of superoxide dismutase(SOD) activity was similar to that of GSH-Px activity. In case of pretreatment with coenzyme Q_{10}, these enzyme activities were more enhanced by dietary coenzyme Q_{10}. However, there was little difference in catalase activity.

KEY WORDS : coenzyme Q_{10} · lipid peroxidation · adriamycin.

Introduction

In recent years, attention has been drawn to the relation of lipid peroxidation in biological systems to various diseases associated with degenerative changes[1]. The process of uncontrolled lipid peroxidation in biological systems may be associated with the loss of essential polyunsaturated fatty acid, and the formation of toxic hydroperoxide or other secondary products[2]. The hydroperoxides and secondary products formed, if not removed, may react with and inactivate essential proteins, enzymes and nucleic acids[3)4]. Ultimately these processes may cause irreversible damage to the cell. In view of the potential damage that may be caused by free radicals and hydroperoxides, and the possible direct effect of various oxidants on the cellular components, it is important that the cell contains antioxidant defense systems[5]. The biological function of vitamin E in preventing a possible free radical attack on mem-

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brane phospholipids has been widely recognized. Similar protective effects by coenzyme Q administration were reported in in vitro system. Mellors and Tappel[6] showed the inhibitory effect of reduced coenzyme Q6 on light-induced autoxidation of mitochondrial lipids at low oxygen pressure, and Takeshige et al[7] also demonstrated the inhibition by reduced coenzyme Q_{10} of NADPH-dependent malondialdehyde (MDA) formation in bovine heart submitochondrial particles.

It has been assumed that cardiotoxicity, a serious side effect of adriamycin(ADR) has been related to oxygen radical formation[8]. Goodman and Hochestein postulated a reduction-autoxidation cycle for ADR with the formation of oxygen radicals followed by lipid peroxidation as the basis for the cardiotoxicity of ADR. Although the mechanism of ADR-induced cardiotoxicity is unexplained, one probable pathway may be the induction of peroxidation in cardiac lipids[10]. Therefore the present study was undertaken to evaluate the effects of dietary coenzyme Q_{10} on lipid peroxide metabolizing enzyme activities in ADR-treated rats.

Materials and Methods

1. Experimental design

To investigate the effects of coenzyme Q_{10} on ADR-induced cardiotoxicity and lipid peroxidation, two experiments were conducted. In both experiments, experimental rats were divided into 7 groups according to the level of ADR and dietary coenzyme Q_{10}. All rats were adapted to basal diet for for 4 weeks. Thereafter, experiment I was undertaken under the condition of simultaneous administration of ADR and experimental diets for 4 weeks. In experiment 2, rats were fed the experimental diets with ADR administration for 4 weeks after feeding experimental diets without ADR for 4 weeks. Experimental design was described in Table 1.

2. Experimental animal and diets

Animals used were male rats of Sprague-Dawley strain. Weanling rats were fed a basal diet for 4 weeks until they reached about 250 g body weight. Thereafter, they were assigned to 7 experimental groups of 10 rats on the basis of their body weight and were individually housed in hanging stainless steel cages with wire-mesh bottoms. Room temperature was maintained at 20 ± 2 ℃, with a 12-hour light (08 : 00-20 : 00) and 12-hour dark cycle (20 : 00-08 : 00). Feed and tap water were provided ad libitum.

The composition of basal diet is shown in Table 2. Two experimental diets (A1Q1, A2Q1 group) consisted of basal diet containing 0.1g coenzyme Q_{10} per kg of diet. On the other hand, other two experimental diets (A1Q2, A2Q2 group) contained 0.5g coenzyme Q_{10} per kg of basal diet and the others (control, A1Q0, A2Q0 group) contained the basal diet without coenzyme Q_{10}.

3. Biochemical analyses

At the end of each experimental period, rats were anesthetized with ethyl ether after 16-hour fasting. Blood was collectd from abdominal aorta with a heparinized syringe and then centrifuged at 1000 x g for 10 minutes to spearate plasma from the cells. Erythrocytes were washed 3 times with 3 volumes of cold saline-phosphate buffer.

To prepare rat heart homogenate, the minced cardiac muscles were homogenized at 4℃ in 10 volumes (wt/vol) of ice solution containing 225 mM mannitol, 75 mM sucrose, 0.1 mM EDTA and 20 mM tris-HCl (pH 7.4)with a motor-driven Teflon Plotter-Elvehjem homogenizer. The heart mitochondrial fraction was prepared from the homogenate by the modified method of Mela and Seitz[11]. The mitochondrial fraction was resuspe-

Table 1. Experimental design

Experiment	Group	Diet composition	Treatment
1, 2[1)]	C	Basal diet	Saline[4)]
	A1Q0	Basal diet	ADR 1[5)]
	A1Q1	Basal diet + Co Q_{10} 1[2)]	ADR 1
	A1Q2	Basal diet + Co Q_{10} 1[3)]	ADR 1
	A1Q0	Basal diet	ADR 2[6)]
	A1Q1	Basal diet + Co Q_{10} 1	ADR 2
	A1Q2	Basal diet + Co Q_{10} 2	ADR 2

1) Exp. 2 was undertaken under the same condition as Exp. 1 after feeding the experimental diets without administration of ADR for 4 weeks.
2) 0.1 g of coenzyme Q_{10}/kg of diet
3) 0.5 g of coenzyme Q_{10}/kg of diet
4) 1.0 mg of saline/kg of body weight/week
5) 1.0 mg of adriamycin in saline/kg of body weight/week
6) 2.0 mg of adriamycin in saline/kg of body weight/week

Table 2. Formula and chemical composition of basal diet used in Exp. 1 and 2

Ingredient or chemical composition	Content(%)
Ingredient;	
Casein	23.5
Corn starch	40.4
Glucose	11.5
Sucrose	5.8
Butter	5.0
Soybean oil	5.0
α-Cellulose	4.0
Mineral Mixture[1)]	3.5
Vitamin Mixture[2)]	1.0
DL-Methionine	0.3
Total	100.0
Chemical composition;	
Crude protein	20.3
Crude fat	9.3
Total carbohydrate	59.0
Metabolizable energy (kcal/100g)[3)]	416.0

1) The mineral mixture based on the pattern of Rogers and Harper(1965) contained the following (g/100g mixture) : $CaCO_3$ 29.29, $CaHPO_4 \cdot 2H_2O$ 0.43, KH_2PO_4 34.31, NaCl 25.06, $MgSO_4 \cdot 7H_2O$ 9.98, $Fe(C_6H_5O_7) \cdot 6H_2O$ 0.623, $CuSO_4 \cdot 5H_2O$ 0.156, $MnSO_4 \cdot H_2O$ 0.121, $ZnCl_2$ 0.02, KI 0.0005, $(NH_4) Mo_7O_{24} \cdot 4H_2O$ 0.0025, $Na_2SeO_3 \cdot 5H_2O$ 0.0015.
2) 100g of Vitamin mixture contained the following : Vitamin A acetate 50,000 IU, Vitamin D 10,000 IU, Vitamin E acetate 50mg, Vitamin K 500g, Thiamin HCl 120mg, pyridoxine HCl 800mg, Cyanocobalamin 0.05mg, Ascorbic acid 3,000mg, D-biotin 2mg, Folic acid 20mg, Calcium pantothenate 500mg, PABA 500mg, Niacin 600mg, Inositol 600mg, Choline chloride 20,000mg, Riboflavin 400mg
3) Calculated value.

nded before use in above-mentioned tris-buffer (PH 7.4). The mitochondrial suspension was treated with ultrasonicator to ensure membrane disruption prior to assays. For the enzyme assays, the crude homogenate was centrifuged at 100,000 x g for 60 minutes in a Sovall refrigerated ultracentrifuge(Du Pont, U.S.A.) and the supernatant fraction was decanted and used to determine the activities of GSH-Px, SOD and catalase. Lipid peroxide level of plasma or heart mitochondrial suspension using thiobarbituric acid (TBA) was measured by the modified method of Ohkawa et al[12]. 1, 1, 3, 3,-Tetraethoxypropane was used as a external standard, and the level of lipid peroxides was expressed as nmol of MDA.

Glutathione peroxidase activity was measured by a coupled enzyme procedure with glutathione reductase utilizing hydrogen peroxide as substrate [13][14]. For the erythrocyte GSH-Px activity, hemolysate was mixed with an equal volume of Drabkin's reagent to convert all hemoglobin to the stable cyanmethemoglobin form. Superoxide dismutase activity was determined by the method described by Winterbourn et al[15] which measures the percent inhibition of nitroblue tetrazolium (NBT) reduction. For the erythrocytes, hemoglobin concentrations of hemolysates were measured and adjusted to about 10 g per 100ml. Catalase activity was assayed by the method of Aebi[16]. Stock erythrocyte hemolysate containing ca. 5g Hb/100ml by the addition of distilled water was prepared and diluted with 0.05 M phosphate buffer immediately before the assay. Heart homogenate supernatant fractions were also diluted with the same buffer. Protein was determined by the method of Lowry et al[17] using bovine serum albumin as standard. Alternately hemoglobin was measured by the cyanmethemoglobin method[18].

4. Statistical analyses

In the statistical analysis, the treatment effects on both experiment 1 and 2 were followed by one-way analysis of variance and Duncan's new multiple range test[19]. Analysis between experiment 1 and 2 was performed using Student's t-test after transforming the parameter of each group into proportional score pivoted upon the control value of each experiment.

Results and Discussion

1. Effects of dietary coenzyme Q_{10} on lipid peroxide level in ADR-treated rat

The production of lipid peroxides was determined in plasma and heart mitochondria of rats as influenced by ADR treatment and dietary coenzyme Q_{10}. There were significant differences in lipid peroxide values among 7 experimental groups in both experiments as shown in Table 3. This indicated that both dietary coenzyme Q_{10} and ADR administration influenced on lipid peroxidation of rat.

In the first experiment, lipid peroxide value of plasma was elevated by ADR treatment. The combined use of ADR and dietary coenzyme Q_{10} reduced this value, but not significantly. Also, the lipid proxide value of rats with coenzyme Q_{10} was not significantly different compared with that of control rats. In case of heart mitochondria, only higher dose treatment of ADR markedly increased the lipid peroxide value. But higher dose group of ADR was significantly decreased in the lipid peroxide value according to coenzyme Q_{10} supplementation. In the second experiment, ADR treatment greatly affected on lipid peroxide value of plasma. This effect was modified, even if not significantly, by dietary coenzyme Q_{10}. The tendency of changes in heart mitochondrial fraction was similar to that in plasma. That is, lipid peroxide value of mitochondrial fraction was significantly increased by ADR treatment, but dietary

Table 3. Effect of dietary coenzyme Q_{10} on lipid peroxide values of ADR-treated rat in Exp. 1 and 2

Group	Plasma (MDA nmol/ml)		Heart mitochondrial fraction (MDA nmol/mg protein)	
	Exp.1	Exp.2	Exp.1	Exp.2
C	$2.14\pm0.45^{a1,2)}$	2.10 ± 0.80^{a}	0.308 ± 0.053^{a}	0.326 ± 0.053^{a}
AlQ0	$3.79\pm0.81^{b)}$	3.96 ± 0.89^{b}	0.400 ± 0.103^{ab}	0.500 ± 0.104^{b}
AlQ1	$2.88\pm0.91^{ab)}$	2.79 ± 1.02^{ac}	0.331 ± 0.039^{a}	0.474 ± 0.050^{b}
AlQ2	$3.09\pm0.65^{ab)}$	2.58 ± 0.96^{ac}	0.395 ± 0.113^{ab}	0.296 ± 0.098^{a}
A2Q0	$3.40\pm1.42^{b)}$	4.21 ± 1.13^{b}	0.633 ± 0.079^{c}	0.556 ± 0.107^{b}
A2Q1	$3.77\pm0.61^{b)}$	3.70 ± 1.00^{bc}	0.514 ± 0.053^{b}	0.296 ± 0.058^{a}
A2Q2	$3.07\pm1.00^{ab)}$	3.29 ± 1.06^{bc}	0.470 ± 0.045^{b}	0.260 ± 0.075^{a}

1) Values shown are the mean±S.D. (Plasma; n=10, Heart; n=5)
2) Values with a common superscript letter within the same column are not significantly different ($P<0.05$).

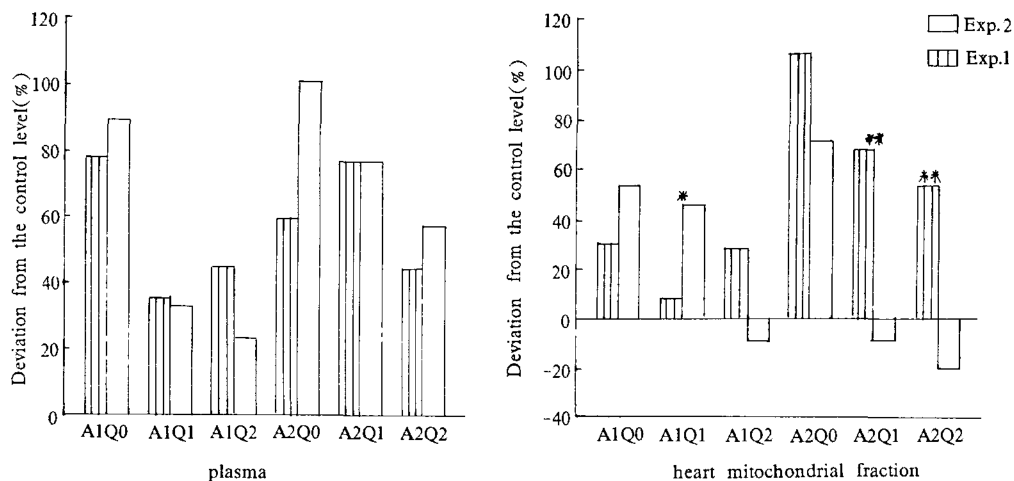

Fig. 1. Comparison of lipid peroxide value of rat in both experiments (* $P<0.05$, ** $P<0.01$).

coenzyme Q_{10} lowered this effect.

Fig. 1 shows the comparison of lipid peroxide values resulted from both experiments. For the convenience and ease of standardization, they presented the values of percentage deviation from each control. According to the present data, pretreatment with coenzyme Q_{10} did not significantly influenced the lipid peroxide value of rat plasma. However, it appeared that pretreatment with dietary coenzyme Q_{10} was more efficient than simultaneous use of ADR and coenzyme Q_{10} in reducing ADR-induced lipid peroxidation of rat heart mitochondrial fraction. Particularly, the degree of decrease was greater in higher dose group of ADR than in lower dose group. On the contrary, mitochondrial lipid peroxide value of AlQ1 group was increased in the pretreated group of coenzyme Q_{10}. As mentioned above, present results clearly demonstrated that ADR treatment significantly raised both the lipid peroxide value of plasma and of heart mitochondria, while this increment was modified by dietary coenzyme Q_{10}(Fig. 1).

Many investigators have reported that ADR

and antioxidants influence upon lipid peroxidation. Mimnaugh et al[20] reported that under in vitro systems, a significant increase in peroxidation by the presence of ADR was measured as early as 15 minutes into the incubations. While, Jackson et al[21] claimed that ADR-treated rabbit hearts did not exhibit significantly increased levels of MDA, product of lipid peroxidation. This finding suggested that free radical generation in the heart may contribute to ADR cardiotoxicity, but that other factors probably play a more important role in the pathogenesis of the myocardial damage. Present study showed that ADR treatment resulted in elevated lipid peroxide levels of plasma and heart, and that lipid peroxidation was an important cause of ADR-induced cardiotoxicity. Some works[10][22] appeared to support this conclusion that ADR treatment induces the cardiotoxicity, probably by lipid peroxidation. Myers et al[10] suggested that lipid peroxidtion may play an important role in ADR toxicity, but prior treatment with tocopherol significantly reduced the ADR-induced cardiomyopathy, probably by blocking lipid peroxidation.

Recently attention has been focused on the possibility of coenzyme Q as antioxidant. The similarity in structure between coenzyme Q and vitamin E may raise such implication. In fact, some investigators demonstrated that coenzyme Q was associated with lipid peroxidation. Marubayashi et al[23] observed that coenzyme Q_{10} pretreatment of ischemic rats could completely reverse impaired mitochondrial function by suppressing an increase in lipid peroxides found in ischemic mitochondria after reperfusion. Several in vitro studies have also shown that reduced coenzyme Q homologs function as antioxidants. Mellors and Tappel [6] stated that when ubiquinone is reduced by the electron transport chain, the ubiquinol formed appears to be as active as α-tocopherol in protecting against lipid peroxidation and could function as one of two principal antioxidants in the mitochondrion. Recently, Suzuki et al[24] suggested that, in protecting against cellular damage, coenzyme Q_{10} not only works by improving ATP synthesis in the electron transport chain but also acts upon the plasma membrae. Although the mechanism of this effect was not entirely understood, the present results were agreed with the reports mentioned above. However it should be recognized that there are differences between present study and previous reports in experimental condition. Compared with reports by Kawasaki et al[25] and Bertazzoli and Chione[26] which indicated that the exogenous coenzyme Q_{10} feeding could concur to protect tissues from the unwanted side effect of drugs acting upon the mitochondria, the present result is considered to be accepted. This effect could also explain the ability of coenzyme Q and related compounds to alleviate certain vitamin E deficiency syndromes.

2. **Effects of dietary coenzyme Q_{10} on lipid peroxide metabolizing enzyme activities in ADR-treated rat.**

The present work was undertaken based on the assumption that one possible mechanism of ADR-induced cardiac toxicity may be associated with peroxidation of cardiac lipids. Thus, lipid peroxide metabolizing enzyme activities were determined to investigate the effect of ADR and dietary coenzyme Q_{10} on lipid peroxidation.

As shown in Table 4, the activities of erythrocyte GSH-Px and SOD were unchanged by injection of ADR and feeding dietary coenzyme Q_{10} in experiment 1. Catalase activity showed higher in groups not treated coenzyme Q_{10} than that in other groups, but only that of A1Q0 group was significantly elevated. This observation indicated that ADR treatment tended to induce slightly ca-

Table 4. Effect of dietary coenzyme Q_{10} on lipid peroxide metabolizing enzyme activities of ADR-treated rat erythrocyte in Exp. 1

Group	GSH-Px (unit/mg Hb)	SOD (unit/mg Hb)	Catalase (unit/mg Hb)
C	63.87±8.84[a1,2)]	2.52±0.52[a]	28.03±2.80[a]
AlQ0	70.11±5.01[a]	3.10±0.66[a]	40.14±5.44[b]
AlQ1	66.99±11.10[a]	3.16±0.77[a]	34.21±5.94[ab]
AlQ2	59.95±9.40[a]	2.83±0.53[a]	32.32±13.32[ab]
A2Q0	62.05±7.36[a]	3.10±0.30[a]	36.36±5.90[ab]
A2Q1	60.29±8.68[a]	2.56±0.26[a]	29.48±13.69[a]
A2Q2	65.20±5.85[a]	2.59±0.39[a]	27.29±2.89[a]

1) Values shown are the mean±S.D. (n=10)

2) Values with a common superscript letter within the same column are not significantly different ($P<0.05$).

Table 5. Effect of dietary coenzyme Q_{10} on lipid peroxide metabolizing enzyme activities of ADR-treated rat erythrocyte in Exp. 2

Group	GSH-Px (unit/mg Hb)	SOD (unit/mg Hb)	Catalase (unit/mg Hb)
C	65.32±5.71[a1,2)]	3.36±1.15[a]	42.50±7.57[a]
AlQ0	58.59±9.54[ac]	3.67±0.41[a]	47.06±4.14[a]
AlQ1	67.74±12.52[a]	3.74±0.87[a]	46.32±11.02[a]
AlQ2	68.31±11.76[a]	3.02±0.39[a]	31.46±7.77[b]
A2Q0	50.63±6.33[bc]	4.24±0.36[a]	50.67±14.15[a]
A2Q1	53.64±9.93[bc]	3.77±0.55[a]	50.00±11.88[a]
A2Q2	53.75±5.72[bc]	4.17±0.50[a]	43.34±9.50[a]

1) Values shown are the mean±S.D. (n=10)

2) Values with a common superscript letter within the same column are not significantly different ($P<0.05$).

talase activity of erythrocyte. In the second experiment, erythrocyte GSH-Px activity was significantly decreased in rats injected ADR at higher level as presented in Table 5. No change in the activity of SOD was observed among the experimental groups. Similarly, there was little difference in catalase activity except A1Q2 group which showed reduction in catalase activity. Fig. 2 shows the comparison of both experiment 1 and 2 in lipid peroxide metabolizing enzyme activities of erythrocyte. In GSH-Px activity, A2Q2 group of experiment 2 was significantly decreased compared with that of experiment 1. The activity of erythrocyte SOD was influenced by pretreatment of dietary coenzyme Q_{10} though there was no consistent tendency. On the whole, it was difficult to find a consistent trend although the present results were slightly influenced by ADR treatment and dietary supplementation of coenzyme Q_{10}. In the present study, there was a tendency of higher erythrocyte catalase activity of ADR-treated rats. But dietary supplementation of coenzyme Q_{10} did not enhanced lipid peroxide metabolizing enzyme activities. Table 6 and 7 show the lipid peroxide metabolizing enzyme activities such as GSH-Px, SOD and catalase in rat heart. In the first experiment, there were generally significant differences among the experimental groups. But catalase activity was not altered by ADR treatment and dietary supplementaion of coenzyme Q_{10}. There was a considerable

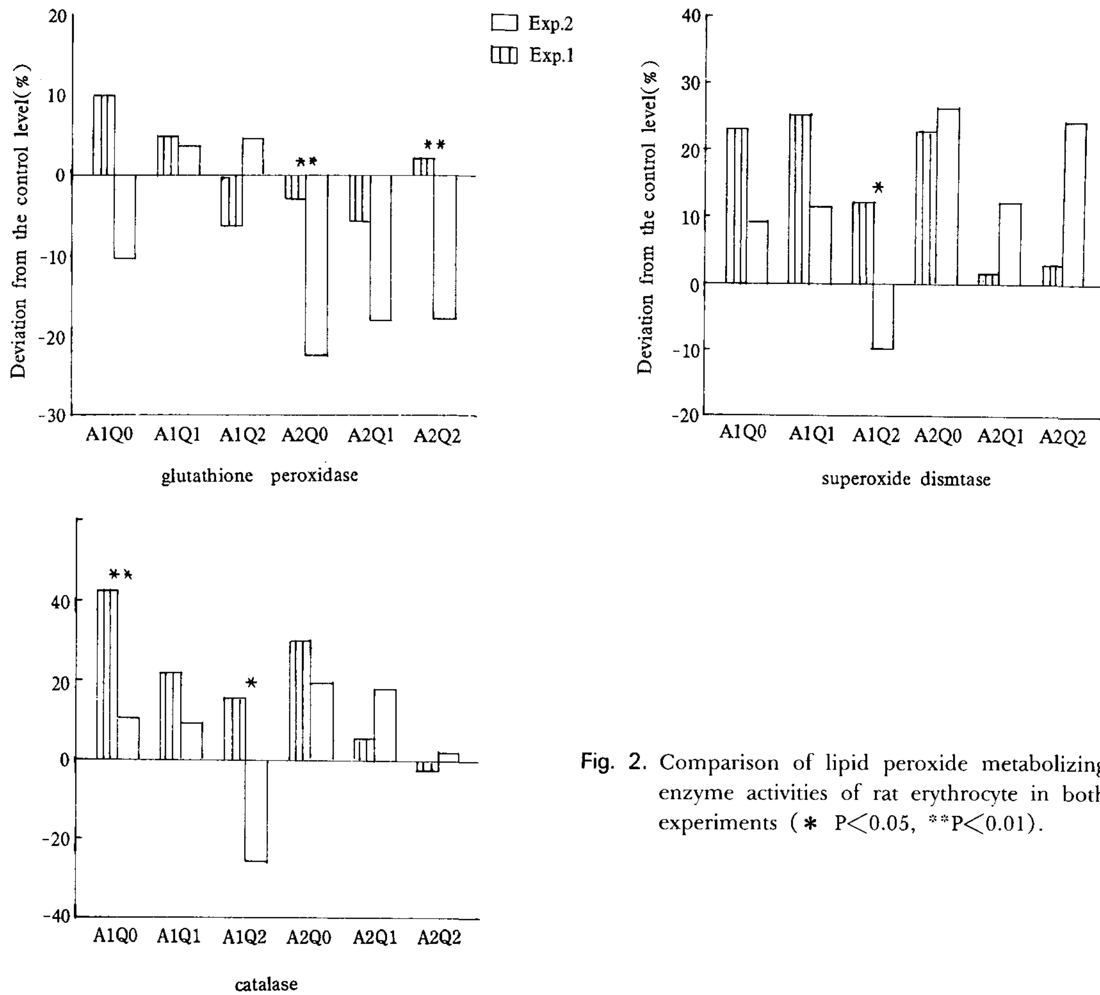

Fig. 2. Comparison of lipid peroxide metabolizing enzyme activities of rat erythrocyte in both experiments (* $P<0.05$, ** $P<0.01$).

effect of dietary coenzyme Q_{10} on GSH-Px activity of rat heart. Dietary supplementation of coenzyme Q_{10}, particularly at higher level, enhanced the heart GSH-Px activity. The activity of SOD was significantly raised by ADR treatment. And with increasing dietary coenzyme Q_{10} level this enzyme activity was more elevated. However, catalase activity was not significantly different among the experimental groups. In the second experiment, the tendency of changes in lipid peroxide metabolizing enzyme activities of ADR treated-rat heart was similar to that in the first experiment. That is, GSH-Px activity tended to be increased by dietary supplementation of coenzyme Q_{10}. The degree of increment of this enzyme was greater in the ADR-treated rats at higher level than that in the ADR-treated rats at lower level. Superoxide dismutase activity was also elevated by ADR treatment, and greatly enhanced by dietary coenzyme Q_{10}. On the other hand, there was little difference in catalase activity. Present data clearly showed that ADR treatment and dietary coenzyme Q_{10} influenced on the activities of GSH-Px and SOD, but not catalase. In the comparison of both experiment 1 and 2, GSH-Px activity of experiment 2 was higher in A1Q1, A2Q2, and A2Q1 groups

Table 6. Effect of dietary coenzyme Q_{10} on lipid peroxide metabolizing enzyme activities of ADR-treated rat heart in Exp. 1

Group	GSH-Px (unit/mg protein)	SOD (unit/mg protein)	Catalase (unit/mg protein)
C	66.14±9.06$^{ac1,2)}$	14.47±1.28^{a}	8.47±1.29^{a}
AlQ0	65.46±8.07^{ac}	17.27±1.23^{b}	8.77±1.20^{a}
AlQ1	65.37±2.04^{ac}	18.45±1.41^{bd}	9.45±1.25^{a}
AlQ2	69.73±7.71^{bc}	20.11±0.81^{cd}	9.80±2.35^{a}
A2Q0	57.39±8.21^{a}	19.95±8.64^{cd}	8.64±1.15^{a}
A2Q1	62.41±7.46^{ac}	20.98±1.41^{ce}	7.56±1.05^{a}
A2Q2	78.75±5.50^{b}	22.88±2.49^{e}	9.75±0.68^{a}

1) Values shown are the mean±S.D. (n=5)
2) Values with a common superscript letter within the same column are not significantly different ($P<0.05$).

Table 7. Effect of dietary coenzyme Q_{10} on lipid peroxide metabolizing enzyme activities of ADR-treated rat heart in Exp. 2

Group	GSH-Px (unit/mg protein)	SOD (unit/mg protein)	Catalase (unit/mg protein)
C	71.21±8.27$^{a1,2)}$	15.71±2.19^{a}	11.52±1.11^{a}
AlQ0	71.78±7.63^{a}	18.06±1.34^{ac}	10.52±1.12^{a}
AlQ1	79.24±4.63^{ac}	18.20±1.50^{ac}	10.12±1.40^{a}
AlQ2	80.47±6.08^{ac}	21.04±2.27^{bcd}	11.12±1.92^{a}
A2Q0	80.50±5.95^{ac}	20.48±1.09^{bc}	11.78±1.39^{a}
A2Q1	84.30±6.44^{bc}	21.76±1.20^{bd}	12.97±1.41^{a}
A2Q2	90.66±2.48^{b}	23.74±2.87^{d}	12.70±1.84^{a}

1) Values shown are the mean±S.D. (n=5)
2) Values with a common superscript letter within the same column are not significantly different ($P<0.05$).

than that of experiment 1. But SOD activity had no difference between both experiments. Catalase activity of experiment 2 groups was significantly increased in A2Q1 group compared with that of experiment 1 groups (Table 4,5,6,7, Fig. 2, 3).

If quinone containing ADR increased lipid peroxidation by a common mechanism involving enhanced reactive oxygen generation, then relative oxygen scavengers should inhibit ADR-stimulated peroxidation. The present study showed that GSH-Px and SOD offer protection against ADR-induced lipid peroxidation. Ekstrom and Ingelman-Sundberg[28)] reported that SOD was an extremely potent inhibitor of cytochromep-450 dependent lipid peroxidation as measured by the formation of TBA-reactive products or lipid hydroperoxides. But they also stated that catalase and hydroxyl radical scavengers were not effective as inhibitors. While Olson et al[29)] demonstrated that the GSH-Px pathway may be of considerable importance in detoxifying formation of cardiac lesions. Similar result was also reported by Noronha-Dutra and Steen[30)] who demonstrated that GSH-Px enzymes are generally accepted as being the main system for the protection of cells against such peroxidation. The ability of GSH-Px to reduce hydroperoxides located in membranes may be faciliated by their cleavage from phospholipids and release into the cytosolic fraction of the cell [31)]. It is generally recognized that mitochondria

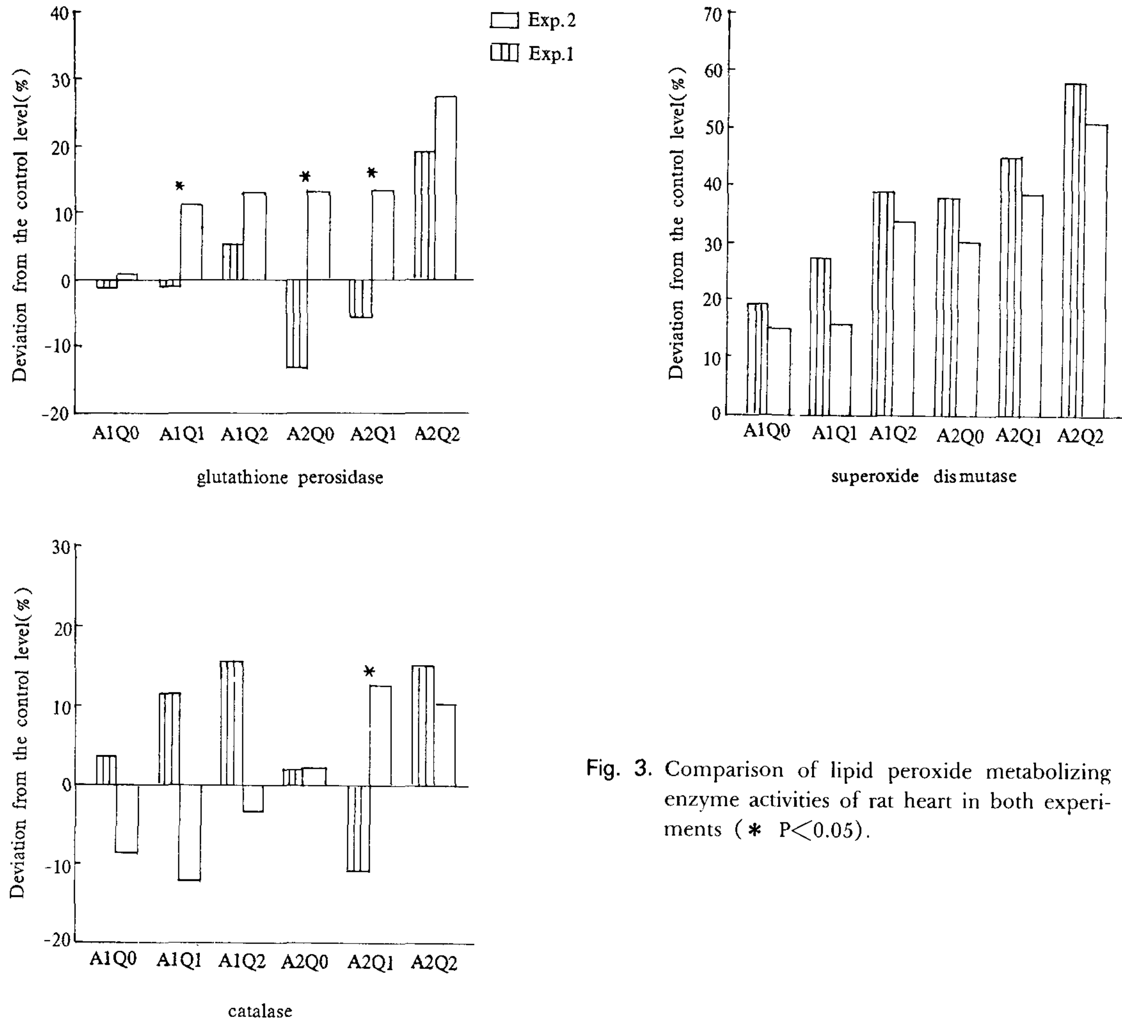

Fig. 3. Comparison of lipid peroxide metabolizing enzyme activities of rat heart in both experiments (* $P<0.05$).

would produce free radicals spontaneously during oxygen reduction and, to counteract this, they have their own mechanism of protection which consists of a specific SOD and GSH-Px enzymes in the matrix space[32]. The two enzyme systems are complementary but, once lipid peroxides are formed, only GSH-Px would be effective. Although the responses shown in the present study were weak, the present results were agreed with the reports mentioned above. Particularly, exogenous coenzyme Q_{10} more enhanced these enzymes.

In conclusion, both dietary coenzyme Q_{10} and ADR administration influenced on lipid peroxidation of rat. It appeared that pretreatment with dietary coenzyme Q_{10} was more efficient than simultaneous use of ADR and coenzyme Q_{10} in reducing ADR-induced lipid peroxidation of rat.

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식이 중의 Coenzyme Q_{10}첨가가 Adriamycin을 투여한 흰쥐의 체내 지질과산화에 미치는 영향 －Ⅰ. 지질과산화물 대사효소에 미치는 영향－

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=국문초록=

식이 중에 첨가된 conzyme Q_{10}이 ADR을 투여한 흰쥐의 체내 지질과산화대사에 미치는 영향을 규명하기 위하여 두가지 실험을 실시하였다.
실험1에서는 basal diet로 적응시킨 후 바로 4주간 실험식이를 공급함과 동시에 ADR을 투여하였으나 실험2에서는 coenzyme Q_{10}이 미리 섭취된 상태하에서 지질과산화에 대한 영향을 관찰하고자 basal diet로 적응시킨 다음 4주간 실험식이만을 급여한 후 다시 4주간 실험1과 같은 방법으로 ADR투여와 실험식이 공급을 병행하였다. 실험군은 실험1과 2에서 모두 ADR 2수준 (1.0mg/kg B.W./week. 2.0mg/kg B.W./week)과 coenzyme Q_{10} 3수준(무첨가군, 0.1g/kg diet 및 0.5g/kg diet)에 의한 6개의 실험군과 basal diet만을 공급하는 대조군을 설정하였다. 본 실험에서 얻어진 결과를 요약하면 혈장과 심장mitochondria 내의 과산화지질 함량은 수준별 ADR 투여에 의해 유의적으로 증가되었고 coenzyme Q_{10} 첨가에 의하여 이러한 경향은 조절되었다. 실험2에 있어서 심장 mitochondria의 과산화지질 함량은 coenzyme Q_{10}의 첨가에 의해 실험1에 비하여 그 감소효과가 더욱 증대되었다. 지질과산화 대사에 관여하는 효소 활성도의 변화를 조사하기위하여 적혈구와 심장조직내에서의 glutathione peroxidase (GSH-Px), superoxide dismutase(SOD)와 catalase 활성도를 측정하였다. 실험1에서 GSH-Px 활성

도는 적혈구 내에서는 차이가 없었고 고수준의 ADR을 투여한 실험군의 심장조직에서만 coenzyme Q_{10}에 의해 유의적으로 증가되었으며, SOD 활성도 역시 적혈구에서는 별다른 변화가 관찰되지 않았고 심장조직 내에서 ADR투여로 증가되었으나 coenzyme Q_{10}의 급여로 그 활성도가 더욱 유도되었다. Catalase의 활성도는 심장조직 내에서는 변화가 없었고 적혈구 내에서 ADR투여로 그 활성도가 증가되었으나 coenzyme Q_{10}의 급여는 그 활성도의 유도효과를 나타내지 못하였다. 실험2의 적혈구내에서는 GSH-Px활성도가 고수준의 ADR의 투여에 의해 유의적으로 감소된 것을 제외하고는 별다른 변화를 나타내지 않았다. 심장조직의 효소활성도에 있어서는 GSH-Px의 경우, 고수준의 coenzyme Q_{10}의 급여에 의해 유의적으로 증가되었으며 SOD활성도는 ADR 투여에 의해 증가되었으나 coenzyme Q_{10}의 공급에 의해 더욱 유도되었다. 그러나 catalase 활성도는 모든 처리군들 사이에서 차이를 나타내지 않았다. 이상의 결과로 미루어보아 ADR투여로 유발되는 심장의 손상은 생체내 지질과산화반응의 유도가 중요한 원인이 되고 이는 coenzyme Q_{10} 급여에 의해 유의적인 억제효과를 나타낼수 있음을 알 수 있다.