DEFICIENCY OF COENZYME Q_{10} IN HYPERTENSIVE RATS AND REDUCTION OF DEFICIENCY BY TREATMENT WITH COENZYME Q_{10}

by

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SUMMARY

Rats which were unilaterally nephrectomized and treated with deoxycorticosterone acetate and saline developed hypertension, and had an increased heart weight. Treatment of these rats with coenzyme Q_{10} effected a lower level of hypertension and normalized the heart weight. The specific activities of the succinate dehydrogenase-CoQ_{10} reductase of leucocytes from these hypertensive rats showed an increase ($P<0.05$) in the deficiency of CoQ_{10}-enzyme activity; treatment with CoQ_{10} lowered ($P<0.05$) the activity to that of the normal group. Leucocytes are convenient and sensitive for monitoring CoQ_{10}-enzymes. A deficiency of CoQ_{10} in hypertension is undesirable for effective bioenergetics and might be corrected by therapy with CoQ_{10}.

INTRODUCTION

Yamagami et al. (1) reported upon a deficiency of coenzyme Q_{10} in leucocytes from patients having hypertension. They found that the specific activity of the succinate dehydrogenase-coenzyme Q_{10} reductase in mitochondria from leucocytes from certain patients with essential hypertension was not only lower ($P<0.001$), but was deficient ($P<0.001$) in comparison with healthy individuals with good nutrition. They summarized information supporting the suggestion that a deficiency of coenzyme Q_{10} may be of some clinical significance in human hypertension.

Igarashi et al. (2) and Yamagami et al. (3) observed a partial but not a total reduction of the experimental hypertension in rats, which is induced by

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deoxycorticosterone acetate and saline, when such rats were treated with coenzyme Q_{10}. Igarashi et al. (2) investigated the content of sodium and potassium in the plasma and in the tissues of these hypertensive rats, and found that the Na/K ratio was higher in the hypertensive than in the normal rats, and that the

ratio decreased with treatment with coenzyme Q_{10}. Yamagami et al. (3) observed that a component of the "antihypertensive" action of coenzyme Q_{10} might be based on the decrease of the hypersensitivity of the peripheral vessels to norepinephrine.

The specific activities of the succinate dehydrogenase-coenzyme Q_{10} reductase in mitochondrial preparations from the leucocytes, liver, kidney, and heart from these hypertensive rats have been determined, and after such rats were treated with coenzyme Q_{10}.

MATERIALS AND METHODS

Thirty-five rats, weighing 180-200 g, were divided into three groups. Twelve rats constituted a normal control group, and were fed a customary laboratory diet. Another group of 12 rats were unilaterally nephrectomized, and were orally treated with 0.9% saline, and 25 mg/kg of deoxycorticosterone acetate (DOCA) by intramuscular injection once a week to induce hypertension. Hypertension was similarly induced into a third group of 11 rats which were orally treated with coenzyme Q_{10} dissolved in corn oil. The dose of coenzyme Q_{10} was 50 mg/kg during the first 4 weeks and then the dose was increased to 100 mg/kg for the fifth and sixth weeks. The systolic blood pressure was recorded every week as described (3). The rats were sacrificed after 6 weeks by decapitation, and whole blood, hearts, kidneys, and livers were removed for enzyme assays.

The blood samples from the rats were processed and assayed as described by Nakamura et al. (4) for the determination of the specific activities of the succinate dehydrogenase-coenzyme Q reductase, and the tissue of the hearts, kidneys, and livers were processed essentially as described by Littarru et al. (5) for the enzyme assay.

RESULTS

Yamagami et al. (3) described studies on the reduction by coenzyme Q_{10} of experimental hypertension in rats which is induced by deoxycorticosterone and saline. They also related their studies to the literature and the citations and relationships are not herein repeated. They showed the partial but not complete control by coenzyme Q_{10} of hypertension in this animal model. The systolic blood pressure was elevated in both the untreated and CoQ_{10}-treated groups ($P < 0.001$) in comparison with that of the normal control group. This induced hypertension

was partially lowered ($P<0.05$) by the treatment with coenzyme Q_{10} and confirmed, in principle, data reported by Igarashi et al. (2).

The mean body weights in the normal control group was about 321 g, about 262 g ($P<0.001$) in the untreated hypertensive group, and about 266 g ($P<0.001$) in the CoQ_{10}-treated group. It was particularly noted that the mean weights of the hearts of the non-treated hypertensive group was greater ($P<0.05$) than that of the normal control group, and that treating these hypertensive rats with coenzyme Q_{10} apparently prevented the enlargement of the heart and its increase in weight.

The data on the specific activities and the percent deficiencies of enzyme activities of the succinate dehydrogenase-coenzyme Q reductase (CoQ_{10}-enzyme) for the leucocytes, livers, kidneys, and hearts of the three groups of rats which were sacrificed after the test period of 6 weeks are in Table 1.

The percent deficiency of the coenzyme Q_{10}-enzyme of the livers of the CoQ-treated hypertensive rats was lower ($P<0.01$) than that of the normal rats and that of the untreated controls. The livers of the normal control rats appeared deficient in CoQ_{10}, and such deficiency was largely corrected by the administration of CoQ_{10}. Similarly, the kidneys of the normal control rats also appeared

Table 1. DATA ON SUCCINATE DEHYDROGENASE-COQ REDUCTASE OF RAT TISSUES

Groups	Specific Activity	Specific Activity with CoQ_3	Activation Coefficient	% Deficiency CoQ_{10}-Enzyme Activity
BLOOD				
Normal	1.87±0.30	2.59±0.24	42.17±7.68	27.00±3.60
Hypertensive	2.70±0.30	4.63±0.46	76.00±8.63	41.42±3.19
Hypertensive-CoQ_{10} Treated	3.09±0.34	4.51±0.55	47.82±9.70	29.09±5.02
LIVER				
Normal	38.47±2.99	73.63± 4.78	95.25±9.50	47.42±2.86
Hypertensive	42.78±5.59	85.81±14.99	95.42±6.64	48.25±1.59
Hypertensive-CoQ_{10} Treated	71.17±8.02	102.34± 8.01	51.82±8.49	32.18±3.59
KIDNEY				
Normal	53.08±3.72	94.08±6.51	78.08±4.97	43.42±1.92
Hypertensive	78.05±7.29	124.68±6.41	66.08±8.12	37.83±3.62
Hypertensive-CoQ_{10} Treated	93.64±7.76	138.86±9.43	50.91±4.33	33.18±1.93
HEART				
Normal	107.79±11.46	145.43±11.46	39.42±6.89	26.08±4.03
Hypertensive	133.21± 9.24	195.49±14.09	49.25±4.34	32.50±1.94
Hypertensive-CoQ_{10} Treated	148.18± 8.15	195.86± 8.34	35.36±4.78	25.18±3.01

Values are Mean ± S.E.

deficient in coenzyme Q_{10} and which was substantially absent in the CoQ_{10}-treated rats. The expression "normal" rat is relative for specific reasons; it has been previously observed (6) that so-called normal animals which are maintained on ordinarily purchased diets are not necessarily normal in respect to saturation with CoQ of CoQ_{10}-enzymes in the tissue, and probably in other nutritional aspects. As the levels of coenzyme Q_{10} varies in those tissues of rats which are important to the pathogenesis of the hypertension, the degree of hypertension to be elicited when such "normal" rats are treated with DOCA-saline may be expected to vary.

In the leucocytes of the blood of the untreated hypertensive rats, the greatest increase in the percent of deficiency of CoQ_{10}-enzyme activity was observed. The percent deficiencies in the kidneys and livers showed no difference between the normal rats and the untreated hypertensive rats, but a significant decrease ($P<0.01$) in comparison with normal rats when CoQ_{10} was administered to the hypertensive rats.

The actual level of CoQ_{10}-enzyme activity is the highest in heart tissue and the lowest in the leucocyte preparations from the blood. Regardless of the absence or presence of coenzyme Q_3 in the differential assay, and for all three groups of rats, these relative levels are compatible with previous studies and reflect again the importance of bioenergetics to the function of the heart.

It is meaningful to appraise the data on the percent deficiency of CoQ_{10}-enzyme activity, because this criterion is directly correlated with a deficiency of coenzyme Q_{10} in the tissue from which the mitochondrial preparation was made.

The leucocyte preparations from the hypertensive rats showed a significant deficiency ($P<0.05$) in CoQ_{10}-enzyme activity in comparison with that of the normal control group. The hypertensive rats which were treated with coenzyme Q_{10} did not show a significant deficiency as was observed for the normal control group. Percent deficiencies of 25-30% have been observed for rats maintained on ordinary laboratory diets with no special precautions against oxidation of unsaturated lipids in the diet.

DISCUSSION

The data in Table 1 were obtained using rats with an ordinary dietary background and from a normal supplier where there was no effort before or after the rats were obtained to have truly normal saturation with coenzyme Q_{10} of coenzyme Q_{10}-enzymes within mitochondria and the Golgi apparatus. For example, treatment of hypertensive rats with coenzyme Q_{10} reduced the deficiencies of activity of the CoQ_{10}-enzyme for the livers and hearts to a significant degree ($P<0.01$). However, the hypertensive state did not lead to an increase in the deficiency

of activity in the liver, kidney and heart in comparison with these organs of the normal control group.

The leucocytes of the blood were the most sensitive and revealed a significant increase ($P<0.05$) in deficiency of CoQ_{10}-enzyme activity. The leucocytes of the hypertensive rats which had been treated with coenzyme Q_{10} revealed a sigficant reduction ($P<0.05$) of the deficiency. It is fortunate that the leucocytes show this sensitivity to the hypertensive state in response to treatment with coenzyme Q_{10}, because leucocyte levels can be monitored without sacrifice of the animal.

Whether there is a correlation between the levels of saturation with coenzyme Q_{10} in its enzymes in leucocytes and the lowering of hypertension by treatment with coenzyme Q_{10} is not clear, but it seems reasonable.

Perhaps the hypertensive state increases the need for coenzyme Q_{10} which is not fulfilled by increased biosynthesis but can be provided through treatment with coenzyme Q_{10}.

A new methodology to detect and measure vitamin deficiencies in mammalian tissues has been reviewed by Folkers et al. (7). The methodology is based upon the enzyme activity of a coenzyme-apoenzyme complex in which the vitamin or its coenzyme form is indispensable to the activity of the enzyme complex. The principle of this assay was formulated by Folkers (8) as follows -- "The specific activity of a coenzyme-apoenzyme system is differentially assayed in the absence and in the presence of added coenzyme. A significant increase in the specific activity of the enzyme system in the presence of added coenzyme indicates a deficiency of the coenzyme at its site or of the vitamin in the tissue".

Brin et al. (9) first utilized this principle to determine deficiencies of thiamin. Glatzle et al. (10) similarly studied deficiencies of riboflavin in geriatric patients. Raika and Sauberlich (11) and Krishmaswamy (12) assayed for deficiencies of vitamin B_6 by this principle.

The extension of this principle to a new enzymatic assay for human deficiencies of coenzyme Q_{10} was detailed by Nakamura et al. (13) and this same assay may be used to seek and measure deficiencies of coenzyme Q_{10} in experimental animal tissues including tissues of the hypertensive rats. Generally, the dual assay is performed on the mitochondrial succinate dehydrogenase-coenzyme Q_{10} reductase, but it can also be applied to DPNH-cytochrome c reductase.

Data showing certain deficiencies of coenzyme Q_{10} in biopsies of human hearts were reported by Littarru et al. (14). The specific activity of the succinate-dehydrogenase-coenzyme Q_{10} reductase of the ventricle wall of the human heart was about 123 nmoles/mg/min. Littarru et al. (5) found about the same level (S.A. 141) of enzyme activity for the heart tissue of the rabbit. The specific activity of this CoQ_{10}-enzyme of the normal rats (Table 1) was 108 and

in the presence of coenzyme Q_3, the specific activity was 145. For blood, the specific activity of this CoQ_{10}-enzyme in the leucocytes was found by Nakamura et al. (13) to be 1.56 for healthy persons and that of the normal rats (Table 1) was 1.87. It is apparent that the level of specific activity of this CoQ_{10}-enzyme is approximately the same in humans, rabbits and rats.

It can be suggested that an increased deficiency of coenzyme Q_{10} in the hypertensive state is an undesirable condition for effective bioenergetics and particularly as required for ion transport including sodium. Correction of a deficiency of coenzyme Q_{10} would surely be a desirable contribution to the control of hypertension.

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