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Research Article

BRAIN NEUROTRANSMITTERS IN DIABETIC RATS TREATED WITH COENZYME Q10

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ABSTRACT

Streptozotocin (STZ) -induced diabetes provides a relevant example of endogenous chronic oxidative stress and hyperglycemia. Thus, we evaluated the brain oxidative stress induced by STZ in rats with consequent changes in brain neurotransmitters and examined the potential protective role of coenzyme Q10 (CoQ10) against the changes STZ induced.60 male albino rats were used in this study, divided into four groups (control, coenzyme Q10, diabetic and diabetic treated groups). Fasting blood glucose, brain malondialdehyde (MDA) as oxidant marker and superoxide dismutase (SOD) as antioxidant marker were estimated. Also brain neurotransmitters including noradrenalin, dopamine and serotonin were measured by high performance liquid chromatography (HPLC). The data showed that oxidative stress markers and brain neurotransmitters were elevated in diabetic rats while coenzyme Q10 decreased these values in treated group. We concluded that coenzyme Q10 supplementation may be useful in treatment of brain dysfunction in diabetes.

Keywords: Diabetes, Neurotransmitters, Coenzyme Q10, HPLC, Oxidative stress

INTRODUCTION

Diabetes mellitus is a complex disease associate with peripheral and central complications. These complications include retinopathy, nephropathy and neuropathy. Several investigations have confirmed the role of oxidative stress in developmental diabetic mediated disorders, possibly via the formation of free radicals [1].

Some tissues, especially the brain, are much more vulnerable to oxidative stress because of their elevated consumption of oxygen and the consequent generation of large amounts of ROS[2], which are closely implicated in several diseases of the nervous system including Parkinson's disease, schizophrenia and Alzheimer's disease[3].

Chronic antioxidant therapies may be useful in decreasing the risk of diabetic complications[4], from these antioxidants coenzyme Q10 which acts as an antioxidant, inhibiting lipid peroxidation and scavenging free radicals [5].

Several studies have provided evidence of the potential of CoQ10 in prophylaxis and therapy of various disorders related to oxidative stress [6]; although (to our knowledge) no study investigated the role of coenzyme Q10 against brain dysfunction in diabetes.

Thus, this study aimed to investigate the brain oxidative stress induced by STZ in rats with consequent changes in brain neurotransmitters and examined the potential protective role of coenzyme Q10 (CoQ10) against the changes STZ induced.

MATERIALS AND METHODS

Materials

Chemicals

Noradrenalin, dopamine and serotonin HPLC standards and streptozotocin (STZ) were purchased from Sigma Aldrich Chemicals Company St.Louis USA. CoQ10 capsules were purchased from Arab Company for Pharm. & Medicinal Plants (MEPACO-MEDIFOOD) Enshas-Sharkeya-Egypt. All other chemicals were of HPLC grade and purchased from Sigma.

Experimental animals:

Sixty male albino rats weighing 180-200 g were obtained from the animal house of National Research Center, Giza, Egypt., and fed a standard commercial diet (control diet) purchased from the Egyptian company of oils and soaps. Water was available ad-libitum for acclimatization before starting the experiment, kept under constant environmental conditions at room temperature.

The guidelines of the ethical care and treatment of the animals followed the regulations of the ethical committee of the National Research Centre (NRC).

Methods

Induction of diabetes

STZ was dissolved in 50 mM sodium citrate solution (pH adjusted at 4.5) containing 150 mM NaCl. The solution containing (6.0 mg/100g body weight) was subcutaneously administrated in rats; fasting blood sugar was estimated after 3 days to confirm the development of diabetes mellitus[7].

Experimental design

Sixty male albino rats divided into four groups (fifteen rats in each group) as follow:

Group I (control group): healthy rats received corn oil (10 mg / kg b.w. /day) orally.

Group II (CoQ10 group): healthy rats received CoQ10 (10 mg / kg b.w. /day) orally.

Group III (diabetic group): diabetic rats received corn oil (10 mg / kg b.w. /day) orally.

Group IV (diabetic treated group): diabetic rats received CoQ10 (10 mg /Kg b.w. /day) orally [8].

After 8 weeks, animals were kept fasting for 12 hours before blood sampling, blood was withdrawn from the retro-orbital venous plexus of the eye using a capillary tube, blood was collected in tubes contain sodium fluoride for blood glucose estimation.

Brains were removed quickly and placed in iced normal saline, perfused with the same solution to remove blood cells, plotted on filter paper and frozen at -80°C until used for estimation of other biochemical parameters.

Preparation of tissue homogenate

The frozen tissues were cut into small pieces and homogenized in phosphate buffer (pH 7.4), then centrifuged at 4000 rpm for 15 minutes at 4°C and the supernatant was removed for chemical parameters estimation[9].

Biochemical assays

Fasting blood glucose was determined according to the method described previously [10]. Brain superoxide dismutase (SOD) and malonedialdehyde (MDA) were measured according to the previous methods respectively [11,12]. Brain norepinephrine; dopamine (DOPA) and serotonin (5-HT) were meassured by HPLC method modified from previous method[13].

Determination of Brain Monoamines

Determination of brain norepinephrine, dopamine and serotonin was carried out using high performance liquid chromatography (HPLC) system, Agilent technologies 1100 series, equipped with a quaternary pump (Quat pump, G131A model). Separation was achieved on ODS-reversed phase column (C18, 25 x 0.46 cm i.d. 5 µm). The mobile phase consisted of potassium phosphate buffer/methanol 97/3 (v/v) and was delivered at a flow rate of 1.5 ml/min. UV detection was performed at 270 nm, and the injection volume was 20 µl. The concentration of both catecholamines and serotonin were determined by external standard method using peak areas. Serial dilutions of standards were injected, and their peak areas were determined. A linear standard curve was constructed by plotting peak areas versus the corresponding concentrations. The concentration in samples was obtained from the curve.

Statistical analysis

All data were expressed as mean ± standard error. Data were analyzed using one-way ANOVA using SPSS (Version 12). Duncan's new multiple-range test was used to assess differences between means. Pearson's correlation test was used to assess correlations between means. A significant difference was considered at the level of $P < 0.05$.

RESULTS

The mean value of plasma glucose in diabetic group was significantly increased compared to control group while CoQ10 supplementation decreased this value compared to diabetic group, although it was still significantly increased compared to control one (table :1) .

As shown in table 1, the mean value level of brain SOD was significantly decreased in diabetic group while the mean value of brain MDA was significantly increased compared to control group. In diabetic treated group, the mean value of brain SOD was significantly increased while the mean value of MDA was significantly decreased compared to diabetic group indicating the reduction of oxidative stress by CoQ10 supplementation.

As shown in Table 2, the mean values of brain, norepinephrine, dopamine and serotonin levels in diabetic group were significantly increased compared to control group while CoQ10 supplementation decreased these values compared to diabetic group.

The data of our study indicated that there is a positive correlation between MDA and neurotransmitters as well as a negative correlation between SOD and neurotransmitters (table: 3).

Table 1: Fasting Blood glucose and brain oxidant/antioxidant parameters in different studied groups.

Groups	Glucose mg/dl	SOD U/g tissue	MDA n mol/g tissue
Control group	79.6 ± 3.4	330 ± 2.7	4.8 ± 1.3
CoQ10 group	82.0 ± 2.0 [b]	322 ± 3.1 [b]	4.6 ± 0.9 [b]
Diabetic group	226.2 ± 8.4 [a]	282 ± 3.6 [a]	62.8 ± 4.7 [a]
Diabetic treated group	187.1 ± 3.2 [a, b]	305 ± 2.0 [a, b]	38.6 ± 1.1 [a, b]

Values are mean ± SE

Significant P value < 0.05; a = significant difference compared to control group; b = significant difference compared to diabetic group; n = number of animals = 15

Table 2: Brain neurotransmitters in different studied groups.

Groups	Norepinephrine ng/g tissue	Dopamine ng/ g tissue	Serotonin µg/ g tissue
Control group	730.0 ± 34.4	30.0 ± 1.1	3.8 ± 0.2
CoQ10 group	740.0 ± 6.5 [b]	32.0 ± 1.0 [b]	3.4 ± 0.2 [b]
Diabetic group	940.0 ± 15.1[a]	52.0 ± 2.3 [a]	4.3 ± 0.1 [a]
Diabetic treated group	752.0 ± 14.1 [b]	41.5 ± 0.7 [a, b]	3.6 ± 0.1 [b]

Values are mean ± SE

Significant P value < 0.05; a = significant difference compared to control group; b = significant difference compared to diabetic group; n = number of animals = 15

Table 3: Correlation between neurotransmitters and oxidative stress.

Parameters	Norepinephrine	Dopamine	Serotonin
Glucose r	0.609(**)	0.812(**)	0.337(**)
p	0.000	0.000	0.019
SOD r	-0.646(**)	-0.766(**)	-0.401(**)
p	0.000	0.000	0.005
MDA r	0.729(**)	0.810(**)	0.442(**)
p	0.000	0.000	0.002

** Significant correlation (P<0.05).

DISCUSSION

STZ-induced diabetes provides a relevant example of endogenous chronic oxidative stress and hyperglycemia. Thus, we evaluated the brain oxidative stress induced by STZ in rats with consequent changes in brain neurotransmitters and examined the potential protective role of coenzyme Q10 against the changes STZ induced.

In the current study there was a significant increase in blood glucose level in diabetic group while this value was decreased by coenzyme Q10 supplementation. This result was in agreement with other study[4] which found that coenzyme Q10 decreased serum glucose levels in diabetic rats.

Also, we observed a significant increase in brain MDA in diabetic rats concomitant with a reduction in SOD indicating an elevation of oxidative stress. In contrast, these values were improved after coenzyme Q10 supplementation. These results were in agreement with a previous study[4] which found a generation of free radicals which promotes lipid peroxidation in STZ induced diabetes. They suggested that, coenzyme Q10 regulates oxidative phosphorylation and prevents lipid peroxidation.

Brain neurotransmitters in this study were elevated in diabetic rats which may be related to oxidative stress since a positive correlation was observed in this study between MDA and neurotransmitters concomitant with a negative correlation between SOD and neurotransmitters. This finding was confirmed by other study [13] which indicated that increased brain oxidative stress has been linked to the development of neurodegenerative diseases.

The suggestion that oxidative stress causes oxygen radicals formation with resultant neurodegeneration and possibly plaque formation in the central nervous system, was supported previously[14], while the improvement of brain neurotransmitters in the treated group may be related to the fact that CoQ10 is an antioxidant that scavenges free radicals directly, inhibits biomolecule oxidation and affects antioxidants in vivo [4]. It is also possible that systemic CoQ10 is able to achieve antioxidant effects by an indirect mechanism for example by, restoration of other brain antioxidants [15].

In addition, CoQ10 a fat-soluble, vitamin-like, benzoquinone compound[16] is a mobile compound in the hydrophobic core of the phospholipids bilayer of the mitochondrial inner membrane. It is an essential factor in the electron transport chain where it accepts electrons from complex 1 and 2 and transfers them one at a time to complex 3. It is composed of a redox active quinoid moiety and a hydrophobic tail and serves as an important antioxidant in both mitochondria and lipid membranes [14].

CONCLUSION

Coenzyme Q 10 seems to be a highly promising compound in protecting the diabetic rats against oxidative damage and preventing brain complications such as elevation of neurotransmitters.

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