European Journal of Pharmacology 794 (2017) 15–19

Contents lists available at ScienceDirect

European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar

Beneficial effect of coenzyme Q_{10} injection on nitric oxide -related dilation of the rat aorta

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ARTICLE INFO

Keywords:
NO-dependent relaxation
Coenzyme Q_{10}
Isolated rat aorta
Intravenous administration
Endothelial dysfunction

ABSTRACT

This study examined whether coenzyme Q_{10} can improve nitric oxide (NO)-dependent vasodilatation in the rat aorta after pre-incubation or intravenous administration. In initial experiments, intact isolated aortic rings were incubated with coenzyme Q_{10} or L-arginine. In further experiments, coenzyme Q_{10} was administered intravenously in anesthetized rats, then in 2 h aorta was isolated. In both cases, after preliminary preparation the isolated aortic rings were tested for acetylcholine-induced NO-dependent relaxation. Acetylcholine elicited concentration-dependent relaxation of phenylephine precontracted aortic rings. Relaxant responses to acetylcholine were markedly potentiated after pre-incubation with coenzyme Q_{10} or L-arginine. The maximum relaxant responses (%) were significantly increased from 64.1 ± 5.3 (control) to 89.8 ± 3.0 and 83.6 ± 3.0 (coenzyme Q_{10} and L-arginine, respectively). pD_2 (-lgEC_{50}) value in control study was 5.81 ± 0.28, after pretreatment with coenzyme Q_{10} or L-arginine were 7.59 ± 0.16 and 7.26 ± 0.32, respectively. There was no difference between coenzyme Q_{10} and L-arginine groups. After intravenous administration, the relaxant responses to acetylcholine were significantly increased in coenzyme Q_{10}-treated group (94.2 ± 2.0) compared with controls (68.1 ± 4.4). pD_2 values were also different between control and treatment groups (5.79 ± 0.29 vs. 8.14 ± 0.65, respectively).

Thus, coenzyme Q_{10} improved NO-mediated vasodilation in rat aorta in magnitude close to the effects of L-arginine - substrate for eNOS. Our data first show that exogenous coenzyme Q_{10} through intravenous administration is able to improve rapidly NO-dependent vasodilation in rat aorta, likely due to accumulation of coenzyme Q_{10} in the vessel wall. Improvement of endothelial function can contribute, at least in part, to beneficial effects of coenzyme Q_{10} in cardiovascular diseases associated with endothelial dysfunction.

1. Introduction

Coenzyme Q_{10} is an indispensable component of the mitochondrial respiratory chain in virtually all body cells. Its functional role consists in the transfer of protons through the cell membrane and the formation of the proton gradient for oxidative phosphorylation (Crane, 2001).

The oxidation and reduction of coenzyme Q_{10} can also take place in other cell organelles, such as lysosomes, Golgi and plasma membranes. Ubiquinol (coenzyme Q_{10}-H_2) used at high doses provides antioxidant protection either by interacting directly with free radicals or by causing regeneration of oxidized tocopherol and ascorbate (Crane, 2001; Tsai et al., 2012). The crucial role of coenzyme Q_{10} in the bioenergetic potential of mitochondria and the comprehensive knowledge of its antioxidative properties make it a useful tool for clinical practice. However, in the state-of-the-art the clinical applicability of coenzyme Q_{10} is still open to question (Littarru and Tiano, 2010; Ayer et al., 2015).

The beneficial effects of coenzyme Q_{10} on patients with heart failure and ischemic heart disease were reported by numerous authors (DiNicolantonio et al., 2015; Sharma et al., 2016; Mortensen, 2003). Our experimental studies established that a single intravenous dose of coenzyme Q_{10} after coronary occlusion rapidly and significantly increased coenzyme Q_{10} content in the myocardium and notably reduced the damage of left ventricular myocardial tissue and its functional activity (Ivanov et al., 2014a, 2014b). In addition, coenzyme Q_{10} was found to produce the hypotensive effect (Yang et al., 2015; Ho et al., 2016; Digiesi et al., 1994; Lonnrot et al., 1998). In all probability, the aforesaid activities of coenzyme Q_{10} are related to its ability to

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http://dx.doi.org/10.1016/j.ejphar.2016.11.019
Received 20 June 2016; Received in revised form 8 November 2016; Accepted 9 November 2016
Available online 15 November 2016
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improve energy metabolism and to prevent oxidative stress in myocardial cells. The inhibiting effect of coenzyme Q_{10} on oxidative stress consists in the scavenging of free oxygen species and "recoupling" of oxidative phosphorylation in mitochondria, which significantly decreases superoxide production (Chew and Watts, 2004).

In body tissues (including the myocardial and renal tissues), the nitric oxide (NO)-soluble guanylate cyclase (sGC)-cyclic guanosine monophosphate (cGMP) pathway fulfils an important physiological function, which is significantly impaired in patients with chronic cardiac insufficiency (CCI) (Gheorghiade et al., 2013; Fraccarollo et al., 2014). Disturbances in NO-sGC-cGMP signaling in CCI are secondary to lowered bioavailability of NO and changes in the redox state of sGC, which makes the latter nonresponsive to NO. Correspondingly, the direct increase of sGC activity makes the latter a promising target for pharmacological control.

Recent studies (Littarru et al., 2011; Gao et al., 2012; Watts et al., 2002; Belardinelli et al., 2006) established that coenzyme Q_{10} treatment significantly improves the functional activity of the endothelium, particularly in patients with type II diabetes and ischemic heart disease (Watts et al., 2002). However, the mechanism of coenzyme Q_{10} effect on endothelial function is still obscure and demands further verification and experiment. The aim of the present study is to investigate the ability of coenzyme Q_{10} to improve NO-dependent vasodilation in rat aorta under different experimental conditions (after preincubation and intravenous administration).

2. Materials and methods

2.1. Animals

Twenty two healthy male Wistar rats (obtained from the Institute of Biomedical Problems, Khimki, Russia) were housed separately in cages under a 12:12 h light/dark cycle at 22 °C with free access to tap water and food. All procedures were performed in accordance with the Guide for the Care and Use of Laboratory Animals and with the prior approval of the bioethics committee of Lomonosov Moscow State University.

2.2. Study design

In the first set of experiments, isolated intact aortic rings of rats were incubated with coenzyme Q_{10} and then tested for NO-dependent relaxation. In the second set of experiments, coenzyme Q_{10} was administered intravenously in anesthetized rats, and then in 2 h aorta were isolated and NO-dependent relaxation was tested. The methods for aorta isolation and vessel preparation, and the testing protocols, were the same in both experimental series.

2.3. Vessel preparation

In the first series, Wistar rats (300–350 g) were anesthetized with intraperitoneal injection of chloralhydrate (600 mg/kg) and euthanized by cervical dislocation. The chest was rapidly opened, and the descending thoracic aorta then dissected and immersed in ice-cold Krebs bicarbonate buffer solution (118.2 mM NaCl, 4.6 mM KCl, 2.5 mM $CaCl_2$, 1.2 mM KH_2PO_4, 1.2 mM $MgSO_4$, 24.8 mM $NaHCO_3$, and 10.0 mM glucose). The preparations were cleaned of excessive connective tissue, cut into ring segments 3 mm in length and then one of them was used as control, one of them was incubated with coenzyme Q_{10} (0.1 mM), and one of them was incubated with L-arginine (3 mM) into 10 ml organ baths containing Krebs solution bubbled with a mixture of 95% O_2 and 5% CO_2.

Each aortic ring was mounted between two stainless steel hooks. The force of contraction was measured with an isometric force-displacement transducer and registered on a physiograph (Rikadenki; Hugo Sachs Elektronik March-Hugstetten, FR, Germany) using a transducer (K30; Hugo Sachs Elektronik KG). Each experiment was performed on rings prepared from different rats.

2.4. Preparation of animals

In the second series of experiments, male Wistar rats (n=12, 300–350 g) were anaesthetized with intraperitoneal chloralhydrate injection (400 mg/kg) and placed on a heated surgical pad at constant body temperature 37 ± 0.5 °C. Water soluble coenzyme Q_{10} at 30 mg/kg (30 mg/ml, Kudesan solution; JSC Akvion, Moscow, Russia) or saline (0.9% NaCl, 1 ml/kg) were administered intravenously via a polyethylene cannula inserted into the femoral vein, immediately after cannulation. After 2 h of drug administration, the animals were anaesthetized by chloralhydrate overdose (600 mg/kg, intraperitoneally) and decapitated in accordance with the Guide for the Care and Use of Laboratory Animals and with the prior approval of the bioethics committee of Lomonosov Moscow State University. The descending thoracic aorta was carefully excised and prepared as described above. The dose 30 mg/kg was chosen on the basis of our previous studies that shown the cardio- and neuroprotective effectiveness of coenzyme Q_{10} intravenously injected (Ivanov et al., 2014a, 2014b; Belousova et al., 2016), 2 h time point was chosen on the basis of our pharmacokinetic data on the distribution of coenzyme in organs and tissues. Even in 15 min after i.v. administration of coenzyme Q_{10} its level statistically significantly increased in the heart by 45% and in the brain – by 35% (Kalenikova et al., 2016). So, we assumed that level of coenzyme Q_{10} in the aortic wall including endothelium increased by the same level, at least.

2.5. NO-dependent relaxation after precontraction by phenylephrine

The aortic rings were initially equilibrated for 60 min at 37 °C with a resting tension of 2.0 g. At the start of each experiment, the rings were first contracted with phenylephrine (0.3 µm) to validate the vascular smooth muscle contractile function. The presence of intact endothelium in vascular preparations was confirmed by clear relaxation responses (over 60% relaxation) to 3 µm acetylcholine in precontracted rings. The preparations were then washed out three times with fresh bathing media every 15 min. After complete washout of acetylcholine and phenylephrine from the organ bath, the rings were again precontracted with 0.3 µm phenylephrine, and after a steady-state tension was reached, increasing concentrations of acetylcholine (0.001–30 µm) were cumulatively added to the organ bath. Each concentration of acetylcholine was added only when the response to the previous dose was stable.

At the beginning of each experiment, all rings were pretreated with diclofenac (1 µm, an inhibitor of cyclooxygenase) for 30 min to prevent the generation of vasoactive prostanoid metabolites. In the first experimental series, either coenzyme Q_{10} (0.1 mM) or L-arginine (3 mM) was added to organ baths for 20 min before investigation of relaxant responses to acetylcholine, and then acetylcholine was tested in the presence of coenzyme Q_{10} or L-arginine. Some rings were incubated for 20 min in the absence of drugs as controls. In the second experimental series the rings were tested without pre-incubation (after *i.v.* administration of coenzyme Q_{10} or saline).

2.6. Drugs

The following drugs were used: acetylcholine chloride, (ACROS Organics, New Jersey, USA.), diclofenac (Voltaren injection solution; Novartis, Basel, Switzerland), phenylephrine and L-arginine (Sigma Chemical Co., St. Louis, MO, USA), coenzyme Q_{10} (30 mg/ml, Kudesan solution; JSC Akvion, Moscow, Russia). Stock solutions were made by dissolving the compounds in distilled water. All solutions were freshly prepared before use and protected from light.

2.7. Data analysis

All data are expressed as mean value ± S.E.M. of n experiments. Relaxations were expressed as the percentages relative to the precontraction induced by phenylephrine (0.3 µm). The logarithm of the acetylcholine concentration producing 50% of the maximum relaxant response (EC_{50}) was calculated by linear regression analysis, and the maximum relaxant response (E_{max}) was determined. E_{max} =100% indicates complete reversal of phenylephrine precontraction. Statistical significance was analyzed by Student's t-test or by 2-way ANOVA for repeated measures when the dose-response curves were compared. Differences at $P < 0.05$ were considered statistically significant. In isometric tension experiments, sample size (n values) equals the number of rats from which aortic rings were obtained.

3. Results

3.1. Vasodilator responses of thoracic aorta

3.1.1. In vitro Coenzyme Q_{10} studies

Phenylephrine at submaximal concentration of 0.3 µm induced a steady tone in rat endothelium-intact aortic rings. Acetylcholine elicited a concentration-dependent relaxation of rat aortic rings. Concentration-response curves of acetylcholine-induced vasorelaxation are shown in Fig. 1. The maximum relaxation was obtained at a concentration of 30 µm acetylcholine. After exposure to coenzyme Q_{10} (0.1 mM) or L-arginine at 3 mM for 20 min, the relaxant responses to all concentrations of acetylcholine were markedly potentiated (Fig. 1). E_{max} was significantly increased from 64.1 ± 5.3 in the control group to 89.8 ± 3.0 and 83.6 ± 3.0 in the coenzyme Q_{10} and L-arginine groups, respectively ($P < 0.05$). Exposure to both coenzyme Q_{10} and L-arginine also caused a leftward shift of the concentration-relaxation curve for acetylcholine. The negative logarithm of EC_{50} (pD_2) value in the control study was 5.81 ± 0.28. After pretreatment with coenzyme Q_{10} and L-arginine, pD_2 values were 7.59 ± 0.16 and 7.26 ± 0.32, respectively ($P < 0.005$ vs control). There was no difference between the coenzyme Q_{10} and L-arginine groups. (Table 1).

3.1.2. In vivo Coenzyme Q_{10} studies

Concentration-response curves of acetylcholine-induced vasorelaxation are shown in Fig. 2. The maximum relaxation was obtained at 30 µm acetylcholine. In the coenzyme Q_{10} -treated group the relaxant responses to all concentrations of acetylcholine were markedly potentiated, with a significantly higher maximum relaxation (94.2 ± 2.0%) than in the control group (68.1 ± 4.4%; $P < 0.005$). The pD_2 value was significantly higher in coenzyme Q_{10} pretreatment group (8.14 ± 0.65) compared with the control group (5.79 ± 0.29, $P < 0.05$) (Table 2).

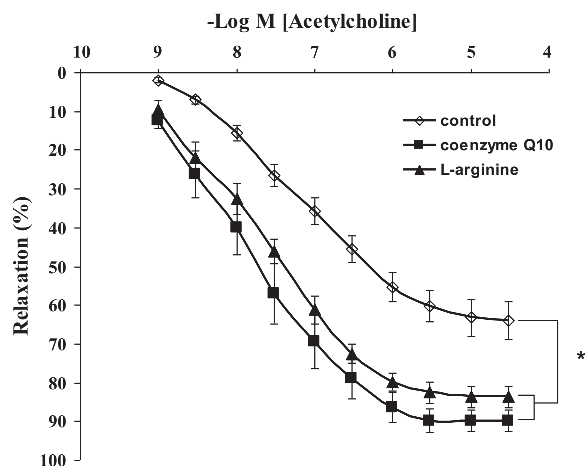

Fig. 1. Effects of coenzyme Q_{10} and L-arginine on the relaxant response to acetylcholine. Concentration-response curves for acetylcholine-induced relaxation in control (▢, n=7), coenzyme Q_{10} (■, 0.1 mM, n=6), and L-arginine (▲, 3 mM, n=7) groups. Data are mean ± S.E.M. of n experiments. *$P < 0.05$ control vs coenzyme Q_{10} and L-arginine.

Table 1
Effects of coenzyme Q_{10} and L-arginine on acetylcholine-induced relaxation.

Groups	pD_2 (-lg EC_{50})	E_{max} (%)	n
Control	5.81 ± 0.28	64.1 ± 5.3	7
Coenzyme Q_{10} (0.1 mM)	7.59 ± 0.16**b**	89.8 ± 3.0**a**	6
L-arginine (3 mM)	7.26 ± 0.32**b**	83.6 ± 3.0**a**	7

The pD_2 (-lg EC_{50}) values and the maximum relaxation (E_{max}) induced by acetylcholine in the absence and presence of coenzyme Q_{10} or L-arginine. Significant differences between control and treatment groups (**a** $P < 0.05$, **b** $P < 0.005$) are indicated. There were no differences between coenzyme Q_{10} and L-arginine groups. Data are mean ± S.E.M. of n experiments.

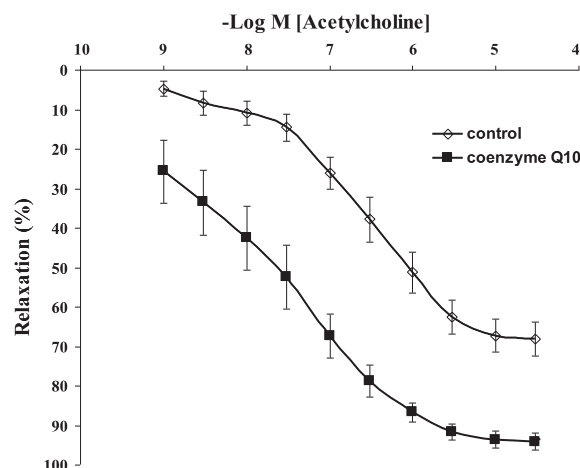

Fig. 2. Effect of i.v. coenzyme Q_{10} administration on the relaxant response to acetylcholine. The concentration-response curves for acetylcholine-induced relaxation in control (▢, n=6) and i.v. coenzyme Q_{10} (■, 30 mg/kg, n=6) groups. Data are mean ± S.E.M. of n experiments.$P < 0.05$ coenzyme Q_{10} vs control.

Table 2
Effects of i.v coenzyme Q_{10} on acetylcholine-induced relaxation.

Groups	pD_2 (-lg EC_{50})	E_{max} (%)	n
Saline (0.9% NaCl, 1 ml/kg)	5.79 ± 0.29	68.1 ± 4.4	6
Coenzyme Q_{10} (30 mg/kg)	8.14 ± 0.65**a**	94.2 ± 2.0**b**	6

The pD_2 (-lg EC_{50}) values and the maximum relaxation (E_{max}) induced by acetylcholine. Significant differences between the control (0.9% NaCl) and treatment groups (**a** $P < 0.05$ and **b** $P < 0.005$) are indicated. Data are mean ± S.E.M. of n experiments.

4. Discussion

Disturbance of the endothelium function is an important pathogenetic factor responsible for a vast array of cardiovascular pathologies (Madamanchi et al., 2005). Endothelial dysfunction is a manifestation of a disbalance in the level of vasodilatory and vasoconstrictor agents. The concentration of nitric oxide ($NO^•$), one of the most important vasodilator agents of the endothelium, is controlled by endothelial $NO^•$ synthase (eNOS), on the one hand, and its inactivation resulting from enhanced production of reactive oxygen species (ROS), on the other hand. The myocardial ischemia-related oxidative stress suppresses the synthesis of $NO^•$; inactivation of the latter is accompanied by generation of peroxynitrite, a potent prooxidant enhancing the damaging effect of ROS (Littarru et al., 2011).

One of hypothetical mechanisms of action of coenzyme Q_{10} in patients with cardiovascular diseases is its ability to improve the

endothelial function and thus exert the vasodilator effect (Kumar et al., 2009; Turunen et al., 2004). The latter is due to the ability of coenzyme Q_{10} to enhance the synthesis and to suppress the inactivation of $NO^{\bullet}$ in the vascular endothelium. Coenzyme Q_{10} inhibits the generation of the superoxide anion in mitochondria and, in doing so, prevents its binding to $NO^{\bullet}$ and subsequent generation of the highly toxic free radical, viz., peroxynitrite (Turunen et al., 2004). It was found (El-Abhar, 2010) that coenzyme Q_{10} can indeed increase the concentration of $NO^{\bullet}$ in gastric mucosa even in the presence of the ulcerogenic effect. The protective activity of coenzyme Q_{10} towards endothelial cells against the background of oxidative stress can also be related to its ability to control the activity of endothelial and inducible $NO^{\bullet}$ synthases providing the optimum (nontoxic) level of $NO^{\bullet}$ (Tsai et al., 2012).

The possibility of correction of endothelial dysfunction by coenzyme Q_{10} was demonstrated in previous experiments with human endothelial cells in vitro (Tsuneki et al., 2013), with rat aortic rings *ex vivo* (Lonnrot et al., 1998) as well as in populational (Gao et al., 2012) and clinical studies in patients with ischemic heart disease (Tiano et al., 2007; Dai et al., 2011) and type II diabetes (Hamilton et al., 2009) receiving long-term per os treatment with coenzyme Q_{10}.

The beneficial effect of coenzyme Q_{10} is directed exclusively on endothelium-dependent vasodilation. No such effect of NO on endothelium-independent vasodilation was observed in mice treated with the NO donor sodium nitroprusside (Gioscia-Ryan et al., 2014) or in human patients receiving nitroglycerine (Dai et al., 2011).

Quite probably, enhanced endothelium-dependent relaxation of the blood vasculature induced by coenzyme Q_{10} treatment reflects the ability of coenzyme Q_{10} to activate NO synthesis in vascular endothelial cells. Supporting evidence in favor of this hypothesis can be derived from the following facts. coenzyme Q_{10} prevented the decrease of NO concentration in human umbilical vein endothelial cells caused by oxidative stress (Dura'n-Prado et al., 2014). Studies by Mugoni et al. (2013) established that the loss of UBIAD1 (non-mitochondrial prenyltransferase responsible for coenzyme Q_{10} synthesis in the Golgi membrane) depleted the cytosolic pool of coenzyme Q_{10} and thus induced ROS-mediated lipid peroxidation in the vascular endothelium.

In Golgi apparatus, coenzyme Q_{10} being an electron carrier, plays the role of an eNOS cofactor by maintaining its “coupled” structure and NO synthesis at a physiological level. On the other hand, UBIAD1 deficiency and low levels of coenzyme Q_{10} may initiate eNOS “uncoupling” and, as a consequence, NO decline and enhanced production of ROS, eventually resulting in serious cell injuries, e.g., lipid peroxidation (Mugoni et al., 2013).

In our studies, enhanced NO-dependent relaxation of rat aorta under the influence of exogenous coenzyme Q_{10} can be attributed to its effect on mitochondria and Golgi endothelial cells and the resulting activation of NO synthesis. The fact that the in vitro effect of coenzyme Q_{10} was commensurate to those of the eNOS substrate L-arginine provides convincing evidence in favor of this hypothesis. Additional evidence was obtained in clinical studies (Regensteiner et al., 2003), which confirmed the ability of L-arginine administered per os over a short period of time to enhance brachial artery FMD and postischemic forearm hyperemia.

The present studies first demonstrate that the endothelial function can be rapidly improved through intravenous administration of coenzyme Q_{10}, which can be regarded as a proof of its antiischemic efficiency. Our earlier experiments showed that intravenous administration of coenzyme Q_{10} promoted fast accumulation of the drug in body tissues (Kalenikova et al., 2016) and, as a consequence, significantly decreased the size of the necrotic zone and improved the functional integrity of the heart and the brain (Ivanov et al., 2014a, 2014b; Belousova et al., 2016).

5. Conclusions

Our data first show that exogenous coenzyme Q_{10} through intravenous administration is able to improve rapidly NO-dependent vasodilation in rat aorta. This finding shows the possibility of rapid implementation of NO-dependent coenzyme Q_{10} effect for therapeutic purposes in acute cardiovascular events associated with endothelial dysfunction. We found that coenzyme Q_{10} improved NO-mediated vasodilation in rat aorta in magnitude close to the effects of L-arginine - substrate for eNOS. This effect was rapid and appeared after both pre-incubation of isolated rat aortic rings with solubilized coenzyme Q_{10} or intravenous coenzyme Q_{10} administration, likely due to accumulation of coenzyme Q_{10} in the vessel wall. Thus, improvement of endothelial function can contribute, at least in part, to the beneficial effects of coenzyme Q_{10} in cardiovascular diseases associated with endothelial dysfunction.

Conflict of interest statement

The authors declare no conflict of interest with respect to this work.

Acknowledgements

This work was supported by the Russian Science Foundation (experiments with intravenously administration) [grant number 14-15-00126]; and by the Russian Foundation for Basic Research (experiments with pre-incubation) [grant number 15-04-05-211].

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