RESEARCH ARTICLE PHARMACOLOGIA

DOI: 10.5567/pharmacologia.2013.529.534

Neurobehavioral Effects of the Intragastric Administration of Coenzyme Q10 Binary Solid Dispersion Tablets in Mice

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ABSTRACT

Objective: The aim of the present study was to evaluate the possible neurobehavioral effects of the administration of Coenzyme Q10 Binary Solid Dispersion (BSD) tablets in mice. **Materials and Methods:** Male Balb/c mice were treated intragastric with 5.7, 11.4 or 17.4 mg kg^{-1} of body weight CoQ10 binary solid dispersion tablets once daily for 7 consecutive days. The animals were submitted to different tests used for screening for psychoactive drugs, such as the open field, light-dark chamber and forced swimming tests. *Rhodiola rosea* L. extract was used as a reference drug (positive control) with known adaptogenic activity. **Results:** Open-field testing resulted in no significant increases of exploratory and locomotor behaviors for all groups treated with CoQ10. A significant increase in swimming time was observed after intragastric administration of BSD with CoQ10. The serum glucose level was significantly higher in the group treated with 11.4 mg kg^{-1} of CoQ10 than in the control group ($p<0.05$). The blood lactate level decreased in relation to an increased dose of CoQ10 and the liver glycogen tended to increase. **Conclusion:** The data indicated that the BSD with CoQ10 tablet is able to induce actoprotective and stimulating effects.

Key words: Actoprotector, behavior, central actions, mice, ubiquinone

Pharmacologia 4 (9): 529-534, 2013

INTRODUCTION

Coenzyme Q10 (CoQ10), also known as ubiquinone or ubidecarenone, is a naturally occurring compound with a ubiquitous distribution in nature. The coenzyme is essential as a bioenergetic because it is a fundamental cofactor in the mitochondrial respiratory chain required for ATP production (Ernster and Dallner, 1995).

The importance of CoQ10 for central nervous system function was corroborated by children in whom a marked CoQ10 deficiency was documented (Ogasahara *et al*., 1989; Boitier *et al*., 1998). The potential usefulness of CoQ10 for the treatment of neurodegenerative and neuromuscular disorders was studied (Shults, 2003; Spindler *et al*., 2009; Mancuso *et al*., 2010). The administration of CoQ10 increases mental concentrations in mature and older animals. It can also increase the brain mitochondrial concentration (Beal, 2002). CoQ10 exhibited beneficial effects when tested in migraine prophylaxis (Sandor *et al*., 2005), treatment of heart failure (Mortensen, 2003) and other cardiovascular diseases (Belardinelli *et al*., 2006) and it also produced a gastroprotective effect (El-Abhar, 2010).

Actoprotectors (from Latin "aktus") were created at the Pharmacology Department of Medical Military Academy (St. Petersburg) as a result of the search for medicines that are able to support motor activity and work capacity (mostly physical) under less than ideal conditions (oxygen deficiency, high environmental temperature, etc.) (Iezhitsa *et al*., 2001). In the 1960s, actoprotector research was performed under the supervision of Prof. V.M. Vinogradov to create drugs that allow unexhausting action which would surpass the level of activity produced by adaptogens, psychostimulators and other known drugs, especially under complicated conditions (Vasil'ev *et al*., 1993). In a broad sense, actoprotectors can be defined as drugs that prevent a decrease in working capacity, even under conditions unfavorable for living and functioning. In contrast to psychomotor stimulants (phenamine, etc.), actoprotectors must not exhaust the energy resources of the organism. The effect of actoprotectors essentially increases the efficiency of the consumption of energetic substrates and stimulates the recovery processes (Morozov *et al*., 2001).

CoQ10 is nearly insoluble in water and is poorly absorbed (T_{max} 5-10 h) by the gastrointestinal tract due to its high molecular weight and poor water solubility (Nepal *et al*., 2010). To overcome the low solubility and bioavailability of CoQ10, various solid formulation approaches have been reported in the literature,

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including binary solid dispersions (Bhandari *et al*., 2007), self-nanoemulsified tablet formulation (Nazzal *et al*., 2002), physical mixture of CoQ10 and microcrystalline cellulose (Terao *et al*., 2006) and liposome (Xia *et al*., 2007). Solid dispersion has been demonstrated as a promising technique for improving the bioavailability of poorly water soluble drugs because it enhances their solubilities and dissolution rates (Shikov *et al*., 2009; Karlina *et al*., 2010). Tablets with binary solid dispersion (BSD) of CoQ10 and polyethylene glycol were used in this study.

Considering the aforementioned pharmacological profile of CoQ10, the present study investigated the possible neurobehavioral effects on mice of the intragastric (i.g.) administration of CoQ10 BSD tablets. A battery of behavioral paradigms that are well validated for the screening of compounds with psychoactive properties were used.

MATERIALS AND METHODS

Animals: Male Balb/c mice weighing 21-24 g were obtained from the Russian Academy of Medical Sciences (Rappolovo, Russia). The mice were maintained under standard laboratory conditions (temperature 22±3°C, relative humidity 50-70%, 12 h light/12 h dark cycle) with free access to a solid pellet (Volosovo, Russia) diet and water ad libitum. They were housed in groups of eight animals per standard cage. All animals were allowed to adapt to the laboratory conditions for 14 days before the behavioral assessment. All procedures were approved by the Institutional Ethics Committee on the Use of Animals, complied with the National Institutes of Health Guide for Care and Use of Laboratory Animals (Publication No. 85-23, revised 1985) and follow the principles of good laboratory practice (GOST R 53434-2009, identical to OECD GMP). Each animal was used only once and all efforts were made to use the minimum number of animals required to obtain consistent experimental data.

Drug preparation: The CoQ10 used in this study was obtained in the form of Valeokor-Q10® tablets provided by LLC NPK Pharmasoft (Moscow, Russian Federation) which contain a binary solid dispersion (BSD) of CoQ10 and polyethylene glycol. Each tablet contains 50 mg of CoQ10. The tablets were ground and dispersed in distilled water. *Rhodiola rosea* L. liquid extract (Kamelia, Moscow region, Russia), standardized by salidroside (0.6%), was dealcoholized and brought to volume in a 100 mL volumetric flask. This extract was used as a reference drug (positive control) with known adaptogenic activity (Panossian and Wikman, 2005).

Behavioral tests: The animals were submitted to different tests that are classically used for the screening of psychoactive drugs, such as the open field, light-dark chamber and forced swimming tests. All tests were carried out during the light period of the cycle (between 10:00 and 17:00 h) and were performed on different days with independent groups of animals. The study was conducted in a sound-attenuated room under red light (12 lux). All studies were recorded using a video camera. The video recordings were later evaluated by an observer who had no knowledge of the treatment that each animal had received.

The male mice were divided into five groups of 8 animals per group. Group 1 served as negative control group, received 0.5 mL distilled water intragastrically (i.g.) by gavage. The mice in group 2 (positive control group) were treated with *R. rosea* extract at the dose 260 mg kg^{-1} b.wt. i.g. The mice in groups 3, 4 and 5 were treated with CoQ10 BSD at doses of CoQ10 of 5.7, 11.4 or 17.4 mg kg^{-1} b. wt. by oral by intragastric tube. All preparations were once daily for 7 consecutive days.

Locomotor and anxiolytic-like activities: The open field test was used to investigate the effects of CoQ10 on locomotor and anxiety-related behavior induced by a novel environment (Prut and Belzung, 2003; Archer, 1973). The apparatus, made of plexiglass, had a 40×40 cm white floor divided into nine squares with 18 holes (2 holes in each square) and 20-cm high white walls. On day 7, forty minutes after the administration of the drug/vehicle, the test began by placing a single mouse in the middle of the arena and permitting it to move freely for 3 min. The observed behavioral parameters were as follows: Horizontal activity (the number of squares crossed) and vertical activity (rearing). The central time, grooming and head dips into holes were indicators of the emotional reactivity of the mouse.

Anxiolytic-like activity: A relevant test system to detect anxiety-related behavior in mice is the light/dark exploration test which uses the aversion of rodents to large, brightly lit spaces (Bourin and Hascoet, 2003). The apparatus consisted of a Perspex box (20×50×20 cm) divided into light and dark chambers of the same size; the chambers were connected by a small door. The dark chamber was entirely black and covered with a solid black plastic top. The light chamber was entirely white and open and was illuminated by a 60 W light bulb. On day 7, forty minutes after the administration of the drug/vehicle, the animal was placed at the center of the illuminated chamber facing the dark area and it was allowed to explore the apparatus for 5 min. The time spent in the light compartment (in %), the latency time until the first passage from the light chamber into the dark chamber and the numbers of entries into each compartment were recorded.

Swimming to exhaustion test: The forced swimming capacity of mice was measured 40 min after drug administration on day 7 using a glass cylinder (45 cm in height, 20 cm in diameter) filled 25 cm high with water (26±2°C). The mice were loaded with a steel washer weighing approximately 5% of their body weight which was attached to the tail. The swimming to exhaustion time was used as the measure of forced swimming capacity. The mice were considered to be exhausted when they failed to rise to the surface of the water to breathe within a 7 sec period. The biochemical parameters of the blood were analyzed after the swimming to exhaustion test. After restraining the mouse, 1.5 μL of blood was collected from the tail vein and applied directly on a strip placed in the glucometer (One Touch Horizon, Life Scan Inc. Milpitas USA, Johnson and Johnson Company). The lactate concentration was measured using an Accutrend Lactate Portable Analyzer and BM Lactate strips (Roche Diagnostics GmbH, Mannheim, Germany). Immediately after the blood was collected, the liver was removed, frozen in liquid nitrogen and stored at -70°C until analysis for glycogen content could be performed. The glycogen content was measured spectrophotometrically using the glucose oxidase method (Chun and Yin, 1998).

Statistical analysis: The data are presented as the Mean±SEM and the statistical analysis was carried out using one-way analysis of variance (ANOVA). The effects of positive control drugs were compared separately against the negative control group using unpaired Student's t-test. The level of $p<0.05$ was used as the criterion of statistical significance. All analyses were performed using the statistical software package (version 5.0, Statsoft, Moscow, Russia).

RESULTS

The body weight of the animals was recorded before the study and again on day 7 and the weight gain was computed. There was no significant difference in body weight between the control group and each treatment group in all studies.

Effects of BSD with CoQ10 on locomotor and anxiolytic-like activities: Open-field testing resulted in no significant increase of exploratory and locomotor behaviors for all groups treated with BSD with CoQ10 (Table 1). The number of grooming episodes was insignificantly decreased for RR group and significantly dose dependent decreased for BSD with CoQ10 groups from 5.4 (Control) to 1.9 (at 17.4 mg kg^{-1}).

Effects of BSD with CoQ10 on anxiolytic-like activity: *R. rosea* extract demonstrated a trend toward an increased likelihood of finding the animal in the light chamber (Table 2). The preference of animals toward the light chamber is an adaptogenic effect of the *R. rosea* extract. Light/dark testing resulted in a significant dose dependent decrease of transitions from 4.4 in control up to 2.5 for the group of BSD with CoQ10 at 17.4 mg kg^{-1}. It is possible that the stress-protective effect of the drug is associated with a normalization of the vegetative processes of the nervous system.

Effects of BSD with CoQ10 on swimming to exhaustion test: The evaluation of a possible adaptogenic effect of CoQ10 using the models of the forced swimming test demonstrated a significant dose-dependent increase in swimming time compared to the control (Fig. 1).

The serum glucose level was dose dependent and significantly higher in the group treated with 17.4 mg kg^{-1} of CoQ10 and reached 120% comparing to the control group ($P<0.05$). The blood lactate level decreased in a dose dependent manner. However, it was significantly lower in the group treated with 17.4 mg kg^{-1} of CoQ10. The liver glycogen content tended to be higher in higher doses of CoQ10.

DISCUSSION

In this study, the effects of the BSD with CoQ10 tablet on the actoprotective activity of the CNS were examined. Typically, the pharmacological assessment of actoprotectors includes the evaluation of stimulation, tonic and stress-protective activities. The most important feature in the pharmacological profiles of actoprotectors is that they increase the efficiency of the consumption of energetic substrates and stimulate recovery processes (Panossian and Wikman, 2005).

The present data demonstrate that, after 7 days of consecutive oral administration, BSD with CoQ10 can significantly increase the swimming time of mice in a dose dependent manner. The swimming time after

Table 1: Effect of BSD with CoQ10 on spontaneous locomotor activity and anxiety-related parameters in the open field test (Mean±SEM)

Groups	No. of squares crossed	Head dips	Rearing	Grooming	Central time (sec)
Control	25.4±4.6	12.5±1.8	9.9±1.5	5.4±0.8	5.6±2.6
R. rosea	19.1±2.1	10.6±1.9	5.3±1.2*	4.6±1.0	2.2±1.2
CoQ10					
5.7 mg kg^{-1}	32.0±2.6	18.7±2.3*	6.3±0.7*	4.3±1.3	5.8±1.2
11.4 mg kg^{-1}	31.3±3.7	18.0.±1.8*	8.0±1.7	3.4±0.4*	4.1±0.7
17.4 mg kg^{-1}	26.3±2.8	24.3±3.0*	15.6±.4.0	1.9±0.4*	3.9±1.1*

Values are significantly different from that of the control group as assessed by Student's t-test at $p<0.05$

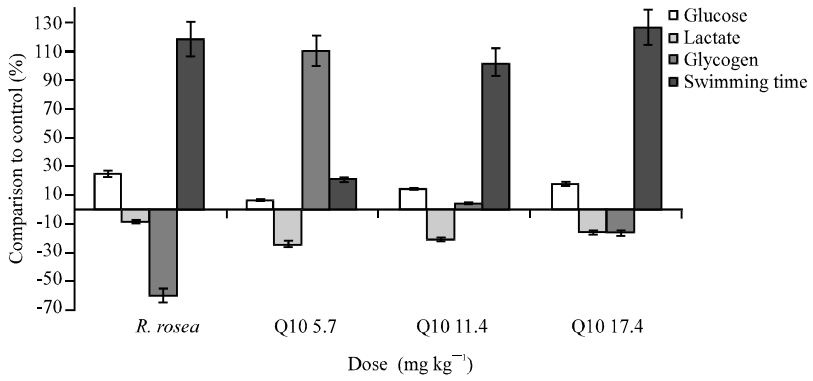

Fig. 1: Variation of glucose, lactate, glycogen and swimming times of mice compared to the control group. Control group received water, *Rhodiola rosea* group received extract of *R. rosea*, groups of BSD with CoQ10 received CoQ10 in doses of 5.7, 11.4 and 17.4 mg kg^{-1}

Table 2: Effect of BSD with CoQ10 on behavioral parameters in the light/dark test (Mean±SEM)

Groups	Time in white (%)	Latency time (sec)	Transitions
Control	17.1±2.8	18.2±6.9	4.4±1.2
R. rosea	43.7±14.0*	49.2±12.8*	1.3±0.4*
CoQ10			
5.7 mg kg^{-1}	18.0±5.3	32.0±9.0	6.0±1.6
11.4 mg kg^{-1}	16.4±6.5	21.7±7.2	4.4±1.9
17.4 mg kg^{-1}	16.2±5.0	19.9±3.2	2.5±0.8**

Values are significantly different from that of the control group as assessed by Student's t-test at $p<0.05$

administration of 17.4 mg kg^{-1} of BSD with CoQ10 was increased by 120% over the control ($p<0.05$) and the effect was similar to that of the classical adaptogen *R. rosea* (Panossian *et al*., 2010). Generally, it is assumed that a decrease in the glucose level indicates increased consumption of energy and that an increase in the lactate level indicates a fatigued condition during prolonged exercise (Jung *et al*., 2004). The blood lactate level was determined primarily as an index of anaerobic metabolism during swimming (Dawson *et al*., 1971). A rapid increase in the blood lactic acid level may be a reflection of an oxygen deficit that is increasing at a high rate. Swimming to exhaustion induces a significantly elevated blood lactate level and the rate at which lactate accumulates in the blood exhibits an inverse relationship with the swimming time after the administration of coenzyme Q10. It has been well established that, during prolonged exercise for 4 weeks, the development of fatigue is closely related to the depletion of glycogen stores in liver tissue (Fu *et al*., 2010). Infusions prepared using fermented leaves of *Bergenia crassifolia* L. and dry extract of *Potentilla alba* L. significantly enhanced the maximum swimming capacity of mice by increasing glucose utilization and by decreasing the lactate level compared to the control treatment (Shikov *et al*., 2010, 2011). Although, *R. rosea* and BSD with CoQ10 at dose of 11.4 mg kg^{-1} showed an increase in swimming times and an increase in the glucose level, neither had an effect on the changes in the lactate and glycogen levels compared to the control treatment. Only at the higher dose of 17.4 mg kg^{-1} of BSD with CoQ10 was a significant increase in the glycogen level registered; The glucose levels of these mice tended to decrease but were not significantly different from those of the controls.

Our results indicate that the antifatigue effect of BSD with CoQ10 is dose dependent in a wide range of experimental doses. However, Fu *et al*. (2010) have reported that the antifatigue effect of CoQ10 is not dose dependent. It is probable that this phenomenon could be attributed to the lower doses used in our study and to the novel formulation in BSD.

To explain the complex mechanisms underlying the actoprotective activity of BSD with CoQ10, the antioxidant effects of CoQ10 should also be considered (Lakomkin *et al*., 2005). Indeed, it is known that exhaustive exercise generates free radicals and that CoQ10 can protect the nervous system from oxidative damage by such free radicals. However, the test used here did not allow us to determine the exact mechanism and further appropriate studies are needed.

The analysis of anxiety-related parameters not revealed marked alterations in the anxiety of the BSD with CoQ10 treated mice. BSD with CoQ10 not showed anxiolytic-like activities that counteracted anxiety in mice subjected to an aversive stimulus in experimental models. The light/dark test is a common test system to detect anxiety-related behavior (Perfumi and Mattioli, 2007). In this study, mice treated with BSD with CoQ10 showed a significant decrease in transitions between the two sections than the control animals. The open field test is utilized to evaluate the animal's emotional state. Animals removed from their

acclimatized cage and placed in a novel environment express anxiety and fear and show alterations in all parameters. The administration of BSD with CoQ10 at a dose of 17.4 mg kg^{-1} induced a significant increase in the head-dip frequency (1.9 times). A number of studies have evaluated the head-dip frequency as an indicator of anxiety: Low values seem to reflect high anxiety conditions, whereas high values indicate a low anxiety level (Casarrubea *et al*., 2010). This factor is also a measure of exploratory activity. Grooming is an important component of a rodent's behavioral repertoire and it is the initial behavioral response to stressful situations and is used by animals to lower arousal (Kalueff and Tuohimaa, 2004). Grooming was decreased in a dose-dependent manner in the BSD with CoQ10 treated mice. This result suggests a decrease in anxiety. All observations support our hypothesis that the administration of BSD with CoQ10 stimulates exploratory activity.

The inconsistent results might be explained by varied bioavailability of different CoQ10 preparations which in turn produces different CoQ10 levels in the plasma and tissue. Because of the hydrophobicity and large molecular weight of CoQ10, the absorption of dietary CoQ10 is slow and limited. Previous studies have suggested that solid dispersion preparations would be best absorbed (Karlina *et al*., 2012).

In conclusion, the present study shows that tablets of BSD with CoQ10 are able to induce actoprotective and stimulating effects in mice, suggesting that CoQ10 may be useful for the development of physical strength and intervention and/or prevention of fatigue. These effects could be associated with a new advanced formulation of CoQ10 in BSD.

Conflict of interest: The Authors declare that they have no conflicts of interest to disclose.

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