doi:10.4149/gpb_2012_052

Short Communication

Increased ubiquinone concentration after intracerebroventricularly-administered ubiquinol to selected rat brain regions

Anna Gvozdjáková[1], Boris Mravec[2,3], Jarmila Kucharská[1], Lubica Lackovičová[2], Katarína Ondičová[3], Martin Tkačov[1] and Ram B. Singh[4]

[1] *Pharmacobiochemical Laboratory of 3rd Department of Internal Medicine, Faculty of Medicine, Comenius University, Bratislava, Slovak Republic*
[2] *Institute of Experimental Endocrinolgy, Slovak Academy of Sciences, Bratislava, Slovak Republic*
[3] *Institute of Pathophysiology, Faculty of Medicine, Comenius University, Bratislava, Slovak Republic*
[4] *Halberg Hospital and Research Institute, Moradabad, India*

Abstract. Brain coenzyme Q_{10} (CoQ_{10}) concentration can influence the activity of several brain regions, including those which participate in the regulation of cardiovascular circadian rhythms, food intake, neuroendocrine stress response, activity and sleep regulation. However, the effect of supplemented ubiquinol (reduced CoQ) into brain regions is not known. This study determined baseline levels of ubiquinone (oxidized CoQ) in various rat brain regions and proved the bioavailability of the liposomal ubiquinol to selected brain regions after its administration into right brain ventricle. Our data indicate that administration of ubiquinol may create the basis for modulation of neuronal activities in specific brain regions.

Key words: Ubiquinol — Ubiquinone — Brain regions

This article is dedicated to Mr. Chopra on the occasion of his 70th birthday with best wishes for a long productive life of the highest quality. Dr. Raj Chopra is president of TISHCON Corp. and Chairman/CEO. He is life fellow of the International College of Nutrition. He has developed almost 10,000 formulations based on nutraceuticals for management of diseases, based on hard scientific data.

Both coenzyme Q_{10} (CoQ_{10}) forms, ubiquinol – reduced CoQ_{10} and ubiquinone – oxidized CoQ_{10}, play a vital role in mitochondrial ATP production and contribute to antioxidant protection in the organism. Ubiquinol is one of the most powerful lipophilic antioxidants, capable of regenerating other antioxidants, such as tocopherol and ascorbate. Ubiquinol gives up electrons to neutralize free radicals, it can inhibit the initiation step and interfere with the propagation step of lipid and protein oxidation (Bentinger et al. 2007). CoQ_{10} is the predominant form in humans, while in rats and mice it is CoQ_9 (Ebadi et al. 2001). In whole rat brain tissue the baseline concentration of CoQ_9 is higher in comparison with CoQ_{10}, yet information about their concentrations in rat brain regions is poor. Localization of fourteen brain regions is shown in Fig. 1. CoQ concentration in brain regions can influence the regulation of heart circadian rhythms, the regulation of food intake, neuroendocrine stress response, regulation of activity and sleep. In diseases or ageing, when the human body produces insuficient amount of CoQ_{10}, the organism calls for its supplementation (Haas 2007; Littarru and Tiano 2010). The authors (Bhagavan and Chopra 2006) reviewed animal data showing that dosage and duration of CoQ_{10} administration are important factors for uptake by brain and heart, as well as by other tissues. Another study found superior bioavailability of the solubilized formulation of both ubiquinone and ubiquinol in plasma compared to unsolubilized CoQ_{10} (Bhagavan and Chopra 2007). The

Correspondence to: Anna Gvozdjáková, Pharmacobiochemical Laboratory of 3rd Department of Internal Medicine, Faculty of Medicine, Comenius University, Sasinkova 4, 811 08 Bratislava, Slovak Republic
E-mail: anna.gvozdjakova@fmed.uniba.sk

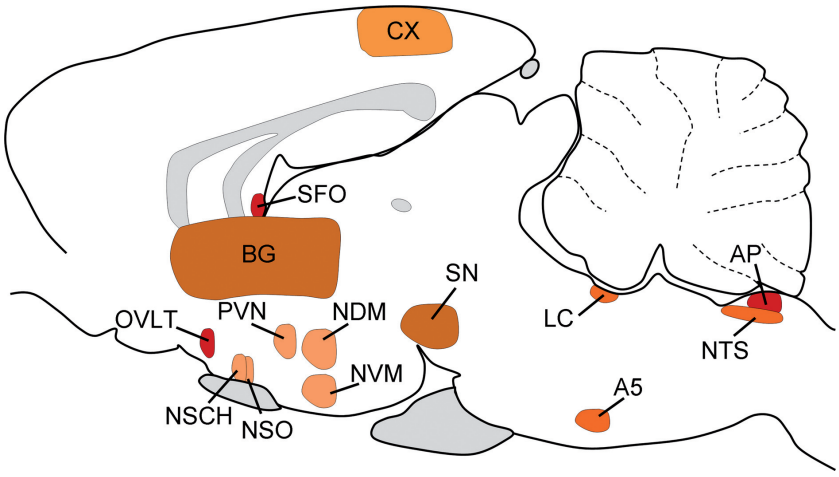

Figure 1. Scheme of rat brain regions. A5, A5 noradrenergic cell group; AP, area posterema; BG, basal ganglia, CX, cortex, LC, locus coeruleus; NDM, nucleus dorsomedialis; NSCH – nucleus suprachiasmaticus; NSO, nucleus supraopticus; NTS, nucleus tractus solitarii; NVM, nucleus ventromedialis; OVLT, organum vasculosum laminae terminalis; PVN, nucleus paraventricularis; SFO, subfornical organ; SN, substantia nigra.

mechanism of supplemented CoQ_{10} effect on brain regions and its function is not clear to date. Our previous studies showed stimulation of brain and heart mitochondrial function in an animal model of Alzheimer´s disease after ubiquinone administration (Horecký et al. 2008). However, the uptake of ubiquinol to brain structures has not been elucidated yet. Concerning this we decided to investigate the uptake of administered ubiquinol by rat brain ventricular regions within the period of 15 to 120 minutes.

Liposomal ubiquinol was administered intracerebroventricularly (40 µl of 10% ubiquinol) into the right lateral ventricle of 3-month-old rats, which were sacrificed at selected time intervals. The control group (represents time zero minutes) consisted of three animals and each of the four ubiquinol groups (represent effect of administered ubiquinol during 15, 30, 60 or 120 minutes) consisted of two animals. Brains were removed after 15, 30, 60 or 120 minutes after ubiquinol administration.

Each brain region has its own special function (Fig. 1). Basal ganglia (BG) participate in signal transduction from the circulation to neurons; organum vasculosum laminae terminalis (OVLT) participate in signal transduction from the systemic circulation to the brain tissue; subfornical organ (SF) is sensory circumventricular organ; nucleus supraopticus (NSO) contains neurons releasing vasopressin and oxytocin into the systemic circulation, regulation of osmolality), nucleus suprachiasmaticus (NSCH) is the main pacemarker regulating heart circadian rhythms; nucleus paraventricularis (PVN) coordinate autonomic, neuroendocrine and immune reactions; nucleus ventromedialis (NVM) regulate food intake; nucleus dorsomedialis (NDM) regulate autonomic nervous system activity and food intake; substantia nigra (SN) regulate motor functions; cortex (CX) is responsible for cognitive function; area posterema (AP) is sensory circumventricular organ; nucleus tractus solitarii (NTS) is main relay station processing visceral and gustatory signals; noradrenergic cell group A5 (A5) regulate autonomic nervous system activity, modulate nociception; locus coerulues (LC) is the main source of brain norepinephrine, regulate vigilance, attention, and stress response. Using the microdissection method we received slices from 14 regions of each brain and used to measure the levels of CoQ (Fig. 1). Each brain region included the following number of slices *per* wet weight (ww): BG (10 slices/4.90 mg ww), OVLT (3 slices/1.20 mg ww), NSO (4 slices/0.72 mg ww), NSCH (4 slices/0.72 mg ww), PVN (6 slices/1.08 mg ww), NVM (10 slices/4.00 mg ww), NDM (10 slices/4.00 mg ww), SN (20 slices/4.00 mg ww), CX (10 slices/9.80 mg ww), NTS (10 slices/1.80 mg ww), A5 (4 slices/0.72 mg ww), LC (6 slices/1.08 mg ww), SFO (3 slices/0.54 mg ww) and AP (3 slices/0.54 mg ww).

Oxidized ubiquinone $CoQ_{10\text{-}OX}$ and $CoQ_{9\text{-}OX}$ concentrations in brain regions were determined by HPLC method using UV detector at 275 nm (Lang et al. 1986) with some modifications (Kucharská et al. 1998). Each value represents the mean concentration of $CoQ_{10\text{-}OX}$ or $CoQ_{9\text{-}OX}$ in samples obtained from two or three rat brain. Concentrations of CoQ are calculated in nmol/g ww. Measurements of $CoQ_{10\text{-}OX}$ (ubiquinone 10) and $CoQ_{9\text{-}OX}$ (ubiquinone 9) concentrations in small samples of SFO and AP were below the limit of the HPLC with UV detection. Excel statistical functions were used for evaluation of mean ± SEM (standard error of

Table 1. Effect of administered ubiquinol on coenzyme Q content in rat brain regions

Brain region	Parameter (nmol/g ww)	Time (min)				
		0	15	30	60	120
BG	$CoQ_{10\text{-}OX}$	3.81 ± 0.15	6.51 ± 0.41	6.03 ± 0.45	9.96 ± 1.55	5.34 ± 1.13
	$CoQ_{9\text{-}OX}$	11.88 ± 0.83	11.87 ± 1.85	12.03 ± 2.05	15.31 ± 1.17	13.62 ± 1.87
OVLT	$CoQ_{10\text{-}OX}$	n.d.	14.87 ± 2.33	13.20 ± 1.23	n.d.	28.30 ± 4.20
	$CoQ_{9\text{-}OX}$	10.83 ± 1.20	14.20 ± 1.63	20.30 ± 3.21	9.00 ± 1.62	22.37 ± 3.06
NSO	$CoQ_{10\text{-}OX}$	n.d.	34.50 ± 7.20	28.00 ± 3.70	n.d.	n.d.
	$CoQ_{9\text{-}OX}$	n.d.	20.39 ± 2.39	20.22 ± 2.88	n.d.	n.d.
NSCH	$CoQ_{10\text{-}OX}$	32.50 ± 1.15	109.39 ± 6.83	39.05 ± 1.93	65.00 ± 6.40	n.d.
	$CoQ_{9\text{-}OX}$	n.d.	n.d.	n.d.	n.d.	n.d.
PVN	$CoQ_{10\text{-}OX}$	n.d.	27.85 ± 4.71	17.81 ± 1.46	34.70 ± 1.90	12.41 ± 1.38
	$CoQ_{9\text{-}OX}$	n.d.	n.d.	n.d.	n.d.	14.81 ± 1.31
NVM	$CoQ_{10\text{-}OX}$	17.05 ± 1.63	75.88 ± 4.53	34.44 ± 2.76	18.35 ± 2.06	5.60 ± 0.64
	$CoQ_{9\text{-}OX}$	8.78 ± 1.24	6.68 ± 1.16	6.61 ± 1.58	5.39 ± 0.43	n.d.
NDM	$CoQ_{10\text{-}OX}$	15.45 ± 1.21	70.00 ± 7.20	32.65 ± 2.05	12.19 ± 2.56	9.17 ± 1.28
	$CoQ_{9\text{-}OX}$	8.89 ± 1.42	8.25 ± 0.54	7.24 ± 0.93	4.26 ± 0.41	5.16 ± 0.18
SN	$CoQ_{10\text{-}OX}$	n.d.	3.18 ± 0.87	3.29 ± 0.66	1.83 ± 0.55	3.62 ± 0.60
	$CoQ_{9\text{-}OX}$	8.34 ± 0.76	8.70 ± 1.11	9.82 ± 1.74	8.56 ± 0.54	11.16 ± 1.16
CX	$CoQ_{10\text{-}OX}$	3.90 ± 0.39	2.35 ± 0.24	2.34 ± 0.35	5.35 ± 0.81	4.31 ± 0.29
	$CoQ_{9\text{-}OX}$	6.51 ± 0.76	6.16 ± 0.78	7.44 ± 0.37	9.31 ± 0.95	4.97 ± 0.58
NTS	$CoQ_{10\text{-}OX}$	n.d.	8.42 ± 0.70	8.64 ± 0.33	15.82 ± 1.29	12.02 ± 1.23
	$CoQ_{9\text{-}OX}$	13.49 ± 0.88	12.04 ± 0.97	27.98 ± 0.68	20.55 ± 1.68	42.98 ± 2.67
A5	$CoQ_{10\text{-}OX}$	16.17 ± 0.63	23.67 ± 1.54	22.11 ± 1.17	n.d.	n.d.
	$CoQ_{9\text{-}OX}$	18.94 ± 0.80	46.83 ± 2.62	28.44 ± 1.53	35.50 ± 1.51	67.28 ± 2.47
LC	$CoQ_{10\text{-}OX}$	33.63 ± 2.16	150.37 ± 10.75	75.85 ± 2.17	98.67 ± 3.55	85.96 ± 3.59
	$CoQ_{9\text{-}OX}$	21.37 ± 1.28	35.59 ± 2.45	21.52 ± 1.34	34.78 ± 2.13	33.00 ± 1.75

Data are expressed as mean ± SEM; n.d., not detectable; $CoQ_{10\text{-}OX}$, ubiquinone 10; $CoQ_{9\text{-}OX}$, ubiquinone 9; BG, basal ganglia; OVLT, organum vasculosum laminae terminalis; NSO, nucleus supraopticus; NSCH, nucleus suprachiasmaticus; PVN, nucleus paraventricularis; NVM, nucleus ventromedialis; NDM, nucleus dorsomedialis; SN, substantia nigra; CX, cortex; NTS, nucleus tractus solitarii; A5, A5 noradrenergic cell group; LC, locus coeruleus.

mean). In this pilot study with a small number of animals in groups,statistical significance was not evaluated. Male Wistar rats were carried out in accordance with the Veterinary and Food Administration of the Slovak Republic and by the Ethics Commitee. The rats were housed at 22 ± 2°C, 45% relative humidity, 12-h light/dark photoperiodicity in rooms with free access to standard laboratory chow and drinking water.

In our study we found differences in CoQ concentrations between individual regions. Administered ubiquinol increased $CoQ_{10\text{-}OX}$ and $CoQ_{9\text{-}OX}$ concentrations in studied regions. Maximum $CoQ_{10\text{-}OX}$ concentration (compared with group without ubiquinol administration – time zero minutes) was found after 15 minutes in the following brain regions: NSO, NSCH, NVM, NDM and LC. After 60 minutes, the maximum $CoQ_{10\text{-}OX}$ concentration was found in BG, PVN and CX, while after 120 minutes in OVLT and in SN. Administered ubiquinol increased $CoQ_{9\text{-}OX}$ concentration in OVLT, NTS and A5 after 120 minutes and had no effect on $CoQ_{9\text{-}OX}$ concentration in NVM, NDM and CX. Our data show higher baseline concentrations of $CoQ_{9\text{-}OX}$ than of $CoQ_{10\text{-}OX}$ in rat brain regions BG, OVLT, SN, CX, NTS, A5, but lower in NSCH, NVM, NDM and LC (Table 1). These different CoQ levels could be connected with individual brain region functions.

The benefit of therapeutic supplementation of ubiquinol in neurodegenerative diseases depends also on its bioavailability. Significantly higher plasma CoQ_{10} concentration was found in subjects aged over 60 years after supplementation with ubiquinol in comparison with ubiquinone (Hosoe et al. 2007). For the first time has been demonstrated beneficial effect of ubiquinol on psychological manifestation in autistic children (Gvozdjáková et al. 2012).

This study determined baseline levels of $CoQ_{10\text{-}OX}$ and $CoQ_{9\text{-}OX}$ in various rat brain regions and proved the

bioavailability of the liposomal ubiquinol to selected brain regions after its administration into the right brain ventricle. Our results may contribute to the elucidation of ubiquinol effects on brain function.

Acknowledgements. This study was supported by the grant of the Ministry of Education VEGA 1/0328/10, and by the Tishcon Corp., USA, by supplying liposomal ubiquinol (Li-QH^{TM}). The technical assistance by A. Štetková is appreciated.

Conflict of interest: There is no conflict of interest.

References

Bentinger M., Brismar K., Dallner G. (2007): The antioxidant role of coenzyme Q: Mitochondrion (Suppl.) **7,** S41–50 http://dx.doi.org/10.1016/j.mito.2007.02.006

Bhagavan H. N., Chopra R. K. (2006): Coenzyme Q10: absorption, tissue uptake, metabolism and pharmacokinetics. Free Rad. Res. **40,** 445–453 http://dx.doi.org/10.1080/10715760600617843

Bhagavan H. N., Chopra R. K. (2007): Plasma coenzyme Q10 response to oral ingestion of coenzyme Q10 formulations. Mitochondrion (Suppl.) **7,** S78–88 http://dx.doi.org/10.1016/j.mito.2007.03.003

Ebadi M., Marwah J., Chopra R. (2001): Mitochondrial ubiquinone (coenzyme Q10): biochemical, functional, medical and therapeutic aspects in human health and disease. Vol. 1. and 2., Prominent Press, Scottsdale, Arizona

Gvozdjáková A., Kucharská J., Babinská K., Lakatošová S., Nakládalová K., Gvozdjáková L., Nakládal D., Koplíková A., Ostrihoňová S., Mego R., Ostatníková D. (2012): Baseline levels of antioxidants, lipid peroxidation and effect of reduced liposomal coenzyme Q10 on psychological manifestations in children with autism. Revue Medicíny v Praxi **10/1,** 11–13 (in Slovak)

Haas R. H. (2007): The evidence basis for coenzyme Q therapy in oxidative phosphorylation disease. Mitochondrion (Suppl.) **7,** S136–145 http://dx.doi.org/10.1016/j.mito.2007.03.008

Horecký J., Vančová O., Kucharská J., Gvozdjáková A. (2008): Coenzyme Q10 supplementation in mitochondrial Alzheimer's disease (Experimental model). In: Mitochondrial Medicine. (Ed. A. Gvozdjáková), pp. 335–337, Springer, Netherlands

Hosoe K., Kitano M., Kishida H., Kubo H., Fujii K., Kitabara M. (2007): Study of safety and bioavailability of ubiquinol (Kaneka QH^{TM}) after single and 4-weeks multiple oral administration to healthy volunteers. Regul. Toxicol. Pharmacol. **47,** 19–28 http://dx.doi.org/10.1016/j.yrtph.2006.07.001

Kucharská J., Gvozdjáková A., Mizera S., Braunová Z., Schreinerová Z., Schrámeková E., Pecháň I., Fabián J. (1998): Participation of coenzyme Q10 in the rejection development of the transplanted heart: a clinical study. Physiol. Res. **47,** 399–204

Lang J. K., Gohil K., Packer L. (1986): Simultaneous determination of tocopherols, ubiquinols, and ubiquinones in blood, plasma, tissue homogenates, and subcellular fractions. Anal. Biochem. **157,** 106–116 http://dx.doi.org/10.1016/0003-2697(86)90203-4

Littarru G. P., Tiano L. (2010): Clinical aspects of coenzyme Q10: an update. Nutrition **26,** 250–254 http://dx.doi.org/10.1016/j.nut.2009.08.008

Received: April 25, 2012
Final version accepted: August 3, 2012