Pharmacology Biochemistry and Behavior, Vol. 64, No. 3, pp. 637–642, 1999

0091-3057/99/$–see front matter

PII S0091-3057(99)00118-5

Coenzyme Q10 Does Not Prevent Oral Dyskinesias Induced by Long-Term Haloperidol Treatment of Rats

OLE A. ANDREASSEN,* CHRISTINE WEBER† AND HUGO A. JØRGENSEN‡

*Department of Physiology, University of Bergen, Bergen, Norway;
†Department of Biochemistry and Nutrition, Technical University of Denmark, Lyngby, Copenhagen, Denmark;
‡Department of Psychiatry, Section Sandviken Hospital, University of Bergen, Bergen, Norway

Received 2 November 1998; Revised 10 May 1999; Accepted May 10, 1999

ANDREASSEN, O. A., C. WEBER AND H. A. JØRGENSEN. *Coenzyme Q10 does not prevent oral dyskinesias induced by long-term haloperidol treatment of rats.* PHARMACOL BIOCHEM BEHAVIOR **64**(3) 637–642, 1999.—Tardive dyskinesia (TD) is a debilitating side effect of long-term treatment with neuroleptics with an unclear pathophysiologic basis. It has been proposed that TD may be a result of neuroleptic-induced oxidative stress. To investigate this hypothesis, we studied if neuroleptic-induced oral dyskinesias in rats, a putative analogue to human TD, could be prevented by the antioxidant coenzyme Q10 (CoQ10). Rats received 16 weeks of treatment with haloperidol decanoate (HAL) IM alone or together with orally administered CoQ10, and the behavior was recorded during and after treatment. HAL significantly increased the level of oral dyskinesias, and the increase persisted for 12 weeks after drug withdrawal. Cotreatment with CoQ10 did not attenuate the development of HAL-induced oral dyskinesia. Despite adequate absorption of orally administered CoQ10, shown by the increased serum levels of CoQ10, no increase of either CoQ10 or coenzyme Q9 was detected in the brain. These results suggest that cotreatment with CoQ10 does not inhibit the development of HAL-induced oral dyskinesias in rats, and that further studies seem to be needed in order to clarify the pharmakokinetics of CoQ10 in rats. © 1999 Elsevier Science Inc.

Neuroleptics Antioxidants Oxidative stress Vacuous chewing movements Tardive dyskinesia HPLC

TARDIVE dyskinesia (TD) is a debilitating side effect of long-term treatment with neuroleptics, characterized by involuntary choreoathetotic movements of the face, mouth, tongue, and occasionally also other parts of the body (35). The syndrome has a delayed onset, and in most cases the dyskinetic movements subside after drug withdrawal, but they may persist. Because TD develops in a large percentage of neuroleptic-treated subjects and is potentially irreversible, the syndrome is of major clinical and ethical importance (64).

The pathophysiology of TD is still poorly understood. It has been suggested that neuroleptic-induced neuronal damage as a result of free radical formation may underlie TD (16). This is supported by findings in the cerebrospinal fluid indicating increased oxidative stress in patients receiving neuroleptics (49), and in TD patients (39). Recently, in vitro experiments have shown that vitamin E protects against haloperidol (HAL)-induced cell death (11), and that neuroleptics induce oxidative stress (10,57). Moreover, there is a close relationship between oxidative stress and glutamate-induced excitotoxicity (19), and excitotoxic mechanisms were suggested to be involved in the development of TD (20,41). Using a rat model of TD, in which a putative TD analogue, vacuous chewing movements (VCM), is induced by long-term HAL treatment, we showed that excitotoxic mechanisms seem to play a role in the development of persistent VCM (4,6). Neuroleptics inhibit mitochondrial energy production (13), which may lead to indirect excitotoxicity, and we reported that impaired energy metabolism produces VCM in rats (4,6).

Based on these findings, the use of neuroprotective agents should be a possible treatment strategy for TD, Vitamin E, a well-known antioxidant (14,48), has in some studies been

Request for reprints should be addressed to Ole A. Andreassen, MD, PhD, Department of Neurology, Massachusetts General Hospital, Warren 411, Fruit Street, Boston, MA 02114.

shown to be beneficial for TD patients [reviewed in (22)]. Another neuroprotective drug candidate is coenzyme Q10 (CoQ10), which has also been used as a protective agent in cardiovascular disease (38,43). CoQ10 is an obligatory redox component of the mitochondrial electron transport system, and has important extramitochondrial antioxidative effects (25,29). Studies in patients with mitochondrial disorders suggest that treatment with CoQ10 results in clinical improvement (30,33,46), and a beneficial effect has also been reported for Huntington disease (27,37). The potential neuroprotective effect of CoQ10 has attracted much attention, and it has been shown that CoQ10 protects against excitotoxin-induced neuronal death in vitro (21,26), and neurotoxin-induced striatal lesions in rats (9,12,54).

The aim of the present study was to investigate whether CoQ10 inhibits the development of VCM induced by 16 weeks of HAL treatment. We also wanted to further describe the bioavailability and brain concentration of CoQ10 after oral administration, because the pharmakokinetics of CoQ10 in rats is not yet fully understood.

METHOD

Animals and Drugs

Sixty female 12-week-old Sprague–Dawley rats (Møllegaard, DK), weighing 200–240 g at the start and 250–320 g at the end of the experiment, were used. The rats were housed under standardized conditions (5), and treated in accordance with the guidelines of the Norwegian Committee for Experiments on Animals. In an acute experiment, three groups of rats (n = 15 per group) were treated with haloperidol (HAL; Janssen, Belgium) 1.0 mg/kg IP; coenzyme Q10 (CoQ10; Vitaline Formulas, Ashland, OR) 200 mg/kg/day in the rat chow, or HAL in combination with CoQ10. The control group (CONT, n = 15) received saline IP and ordinary rat chow. CoQ10 was prepared in the rat chow (Altromin, Germany) and administered to the rats in the morning. The consumption of the food lasted typically 2–3 h. CoQ10 was administered daily for 1 week prior to the IP injections of HAL. After the acute experiment, the rats entered the long-term experiment where the four groups received the same treatment, except that HAL was administered as decanoate 38 mg/kg IM every 4 weeks, and the CONT group received equal volumes of sesame oil IM (Nycomed Pharma, Norway). The long-term treatment lasted 16 weeks, with the last IM injection at week 12. The rats were weighed every 14 days, and the concentration of CoQ10 in the diet was adjusted to keep the daily dose of CoQ10 close to 200 mg/kg/day.

Behavioral Observations

The behavioral observations were the same as previously described in detail (3). Prior to the start of the experiment, the animals were handled daily and habituated to the behavior evaluation procedure for 1 week. During observations, the rats were placed in a clear Perspex cage (25 × 11 × 13 cm), allowing videotaping from all sides simultaneously, and after 1 min of adaptation the behavior was videotaped for 3 min. A trained observer, unaware of the treatment of the rats, scored the behavior while watching the videotapes. A computer with custom-designed software was used, and the following behavioral categories were recorded: VCM, jerking, jaw tremor, immobility, sitting/standing, moving, rearing, and grooming. For the first two behavioral categories, the frequencies were recorded. For the other categories the duration was recorded. The behavior was videotaped before initiating treatment, 1 h after the IP injections in the acute experiment, and the day prior to the IM injections during the long-term treatment, and regularly after cessation of treatment.

Coenzyme Measurements

An additional group of rats, not included in the behavior analysis, was used for drug analysis. Five hours after the morning feeding at the tenth day of CoQ10 administration, rats receiving CoQ10 (n = 4), CoQ10+HAL (n = 4) and control rats (n = 4) were anesthetized with halothane gas. Then, after transcardial puncture, blood samples (5–10 ml) were collected and the brains were removed and frozen at −20°C until analysis. A volume of 0.1-ml serum was extracted after addition of 0.025 ml 1 mg/ml BHT in EtOH, 0.9 ml H_2O, and 2 ml hexane. Then 1.5 ml of the hexane layer was taken to dryness under nitrogen and redissolved in 0.2 ml ethanol, and 10 μl was used for HPLC analysis. The brains were weighed, and then homogenized in 15 ml ice-cold buffer (130 mM NaCl, 1 mM EDTA, 10 mM NaH_2PO_4, pH 7.0) after addition of 0.4 ml 1 mg/ml BHT. One milliliter of the homogenate was extracted with 1 ml 0.1 M SDS, 2 ml ethanol, and 2 ml hexane, and 1.5 ml of the hexane was taken to dryness under N_2, redissolved in 0.5 ml ethanol and 20 μl injected onto the HPLC (51).

The HPLC analysis was performed on a Waters system with Waters 510 pumps, a Beckman Ultrasphere ODS C-18 column, 4.6 mm i.d., 25 cm, 5-μm particle size, a Waters Wisp 717 autosampler, Millenium software and using a Coulochem 5100A electrochemical detector, (Environmental Sciences Assoc., Bedford, MA), equipped with a Model 5020 Conditioning cell set at −750 mV, and a Model 5011 Analytical cell with two electrodes in series, the first set at −750 mV, and the second set at +500 mV. The eluent was ethanol/methanol/iso-

TABLE 1
ACUTE EXPERIMENT

	VCM	Immobility	Move/Rear
CONT	0.0 (0.0–0.0)	0.0 (0.0–0.0)	124.2 (100.3–147.8)
CoQ10	0.0 (0.0–1.0)	0.0 (0.0–0.0)	117.2 (100.3–138.4)
HAL	6.0 (2.0–7.8)*	11.2 (0.0–108.8)*	55.0 (27.0–81.0)*
CoQ10+HAL	5.0 (2.3–7.5)*	75.9 (37.7–92.2)*	39.2 (9.4–67.4)*

VCM = vacuous chewing movements (number per 3 min), immobility and move/rear (s per 3 min). HAL = haloperidol, CoQ10 = coenzyme Q10,CONT = control group. Medians with 25 and 75 percentiles are presented.

* $p < 0.001$ vs. CONT (Mann–Whitney U-test).

propanol 715/245/40 0.1 percent w/v lithium perchlorate at 1.2 ml/min. This method was slightly modified from the method used by Kontush and co-workers (36).

Statistics

Differences in behavior between treatment groups were analyzed with the Mann–Whitney *U*-test. Before statistical analysis of the results of long-term treatment, data obtained at different time points were added, giving one value per animal for the treatment period, and one value per animal for the 16 weeks posttreatment period. The differences in serum and brain levels of coenzymes were analyzed with one-way ANOVA followed by Students *t*-test.

RESULTS

In the acute experiment (Table 1), HAL strongly increased VCM (HAL vs. CONT, $p < 0.0001$), and decreased the level of gross motor activity, shown by a significant increase in immobility (HAL vs. CONT, $p = 0.002$) and decrease in moving/rearing (HAL vs. CONT, $p = 0.0001$). The same significant behavioral effects of HAL was seen in the cotreatment group (HAL+CoQ10 vs. CONT, $p < 0.0001$ for VCM, immobility, and moving/rearing), and 1 week of pretreatment with CoQ10 did not significantly affect any behavioral effect of HAL. Before initiating treatment, no significant differences between the groups were present for any type of behavior, although there was a nonsignificant increase in VCM in the CoQ10 group compared to CONT group.

During long-term treatment (Table 2), HAL significantly increased the VCM level independently of CoQ10 cotreatment (HAL vs. CONT, $p = 0.0007$, CoQ10+HAL vs. CONT, $p = 0.0001$). CoQ10 treatment did not significantly affect any behavior (CoQ10 vs. CONT, n.s.; CoQ10+HAL vs. HAL, NS), although a nonsignificant trend toward a higher number of VCM was present in the CoQ10 group. The HAL-induced decrease in gross motor activity during long-term treatment was much weaker than in the acute experiment, and only sitting/standing was significantly increased (HAL vs. CONT, $p = 0.02$, data not shown). After drug-withdrawal, the increase in VCM induced by HAL persisted for 12 weeks (HAL vs. CONT, $p = 0.04$, CoQ10+HAL vs. CONT, $p = 0.007$). No significant effects of CoQ10 was present after cessation of treatment (CoQ10 vs. CONT, NS; CoQ10+HAL vs. HAL, NS).

The serum and brain measurements of CoQ9 and CoQ10 are shown in Table 3. The CoQ10 treatment (CoQ10 and CoQ10+HAL) increased serum CoQ10 significantly ($p < 0.001$) compared to controls. The redox level of CoQ10 (% reduced Q/total Q) is a measure of the antioxidative potential of the serum CoQ10, as only the reduced form has an antioxidative effect. The redox level of serum CoQ10 was significantly higher ($p < 0.001$) in the control rats compared to the CoQ10-treated groups (57.3 vs. 1.54%, respectively). Apparently, the orally supplemented CoQ10 has not been reduced prior to appearance in the circulation. Serum CoQ9 was significantly higher in control rats compared to the CoQ10-treated groups ($p < 0.005$). No increase in brain CoQ10 was seen upon CoQ10 treatment, despite the increased serum levels.

TABLE 2

VACUOUS CHEWING MOVEMENTS DURING AND AFTER LONG-TERM TREATMENT

	During Treatment VCM	After Drug Withdrawal VCM
CONT	0.5 (0.0–1.0)	0.5 (0.3–1.8)
CoQ10	1.3 (0.2–2.3)	1.7 (0.6–2.4)
HAL	2.0 (1.1–2.8)†	1.8 (0.9–2.5)*
CoQ10+HAL	3.0 (2.0–3.6)†	2.0 (1.3–2.9)*

VCM = vacuous chewing movements (number per 3 min). Medians with 25 and 75 percentiles are presented.

* $p < 0.05$; † < 0.001 vs. CONT (Mann–Whitney *U*-test). HAL = haloperidol, CoQ10 = coenzyme Q10, CONT = control group.

DISCUSSION

The main findings of the present study was that cotreatment with CoQ10 did not attenuate oral dyskinesias induced by long-term HAL treatment of rats, and that the increase in serum levels of CoQ10 after oral administration was not reflected in significantly increased brain levels.

Behavior

An increase in VCM during long-term neuroleptic treatment has been shown in a number of studies (5,18,24,31,58), and VCM is suggested as a putative model of TD in humans. This rodent model has been used to test potential pharmacological treatment regimens for TD (3,5,23,56).

CoQ10 protects against ischemia and reperfusion in the heart (47), and has effect in the treatment of cardiomyopathy (38). This has been related to the antioxidant properties of CoQ10 (25). In addition, CoQ10 is an essential component of the electron transport chain where it serves as an electron donor and acceptor (51), and increases the activity of the mitochondrial electron transport system (44,53). Both oxidative stress and impaired energy metabolism have been related to the pathogenesis of TD (13,31) and VCM in rats, (4,6). Treatment with CoQ10 has been suggested as a rational approach

TABLE 3

CONTENT AND REDOX LEVEL OF COENZYME Q9 AND Q10 IN SERUM AND BRAIN OF RATS TREATED WITH HALOPERIDOL, COENZYME Q10, OR BOTH, VERSUS CONTROLS

Treatment	Serum CoQ9 (μM)	Serum CoQ10 (μM)	Redox level serum CoQ10 (%)*	Brain CoQ9 (nmol/g)	Brain CoQ10 (nmol/g)
CONT	0.34 ± 0.08^{b}	0.11 ± 0.02^{a}	57.3 ± 3.3^{b}	24.5 ± 5.1	10.6 ± 2.4
CoQ10	0.17 ± 0.02^{a}	1.78 ± 0.23^{b}	1.54 ± 0.33^{a}	25.0 ± 2.3	11.3 ± 1.1
CoQ10+HAL	0.20 ± 0.03^{a}	2.66 ± 0.54^{c}	1.54 ± 0.46^{a}	20.7 ± 3.6	9.05 ± 1.63

HAL = haloperidol, CoQ10 = coenzyme Q10, CoQ9 = coenzyme Q9, CONT = control group.

* Redox level: % (reduced Q/total Q). Means ± SEM are presented. Means in columns with different superscripts differ significantly (Students *t*-test).

to slow the progression of neurodegenerative diseases, and it has been shown that CoQ10 produces clinical and biochemical improvement in some mitochondrial diseases (1,45). In patients with Huntington disease, CoQ10 treatment decreased the brain lactate level (37), and tended to improve some aspects of the movement disorder (27). Taken together, these results suggest that treatment with CoQ10 could be beneficial in preventing the development of TD. The present results, which show that cotreatment with CoQ10 does not attenuate oral dyskinesias induced by long-term HAL treatment of rats, indicate that CoQ10 will not be beneficial in the prevention of TD in humans.

Biochemistry

The present results show that oral administration of CoQ10 mixed into the rat chow gives a significant increase in the serum level, reflecting an adequate intestinal absorption. This is in accordance with other studies (61,62). Several authors have found significant protection against neurotoxins after oral administration of CoQ10 in rats, using 10 days of treatment and the same dose as in the present study (9,12,54). Similar protective effects have also been found in mice (8). These findings indicate that the present treatment regimen should exert neuroprotective effects. However, in the present study, no significant increase was found in the two forms of coenzyme Q in the brains of the rats after 2 weeks of treatment. This could be the result if the brain content of CoQ10 was catabolized. The half-life of CoQ10 in brain slices of rats is 90 h (2), and in the present study the brains were removed and frozen immediately after the blood samples were collected. This excludes any degeneration of the brain content of CoQ10.

Previous work questioned whether CoQ10 accumulates in tissues (52), and this might explain the present results. There are, however, several lines of evidence arguing against this. A line of studies in rats have shown that oral administration of CoQ10 results in increased levels in liver and spleen (34,55,60), but some previous studies found not increase of CoQ10 in the brain (61,62). In a recent study, however, a significant increase in the brain content of CoQ10 after 2 months of oral CoQ10 supplementation to 12 months old rats was found (40). This shows that CoQ10 does accumulate in the brain after long-term oral administration to adult rats, and the authors argue that it is possible that a dietary supplementation may restore age-dependent decreases in CoQ10 brain content (40). It is possible that a similar process took place in the adult rats used in the present study.

It could be speculated that the neuroprotective effect of CoQ10 seen in the previous studies (8,9,12,54) could be due to a systemic effect and not a direct neuroprotective effect in the brain. Another possibility is that increased levels of CoQ10 in serum acts as an antioxidant on other components, which easily cross the blood–brain barrier and works as antioxidants within the brain.

To function as an antioxidant, CoQ10 must be reduced to ubiquinol. The CoQ10 responsible for the present increase in serum level was mostly in the oxidized form, which indicates that there was only a small antioxidative potential of the supplied CoQ10 using the present treatment regimen. This is contrary to the results of human studies, where orally administered CoQ10 leads to an increased serum level of reduced CoQ10 (42,59). Thus, differences in the metabolism of CoQ10 may exist between humans and rats, but the reason for this difference is not clear. It could be speculated that the enzyme responsible for reducing coenzyme Q in rats is specific for the Q9 form, which is the most abundant form of coenzyme Q in rats. Most of the coenzyme Q present in the brain of Sprague–Dawley rats is in the Q9 form, and only one-third of the coenzyme pool consist of CoQ10 (8,64). This is in accordance with the present analyses of brain level of CoQ10 and CoQ9. It seems that further studies are needed to further clarify the pharmakokinetics of CoQ10 in rats.

It is interesting that the group of rats receiving HAL in addition to CoQ10 had significantly higher serum levels of Q10 than rats receiving CoQ10 alone. HAL is a known inhibitor of cytochrom P-450 enzymes responsible for metabolism of many drugs (17). The metabolism of CoQ10 is not yet known, but it is possible that it is metabolized via the cytochrom P-450 enzyme system, because other quinones are metabolized by this system (15,28). A HAL-induced inhibition of CoQ10 metabolism could explain the present results. Another issue is that serum CoQ9 was significantly lower in rats receiving CoQ10 supplementation compared to control rats. The reason for this difference is not known, but it could be speculated that it could be due to an inhibition of endogenous CoQ9 synthesis.

Although the present results failed to show that CoQ10 was increased in the brain after short-term oral administration to rats, others have reported that CoQ10 does accumulate in the brain after long-term oral administration to adult rats (41). Based on these findings, the present results that show that cotreatment with CoQ10 does not attenuate oral dyskinesias induced by long-term HAL treatment of rats, indicate that CoQ10 will not be beneficial in the prevention of TD in humans.

ACKNOWLEDGEMENTS

The authors wish to thank Marianne Nævdal for excellent technical assistance and the Professors Kjell Hole and Gunhild Hølmer for helpful discussions and contributions to the manuscript. The research was supported by grants from the Norwegian Research Council, the Danish MRC, the NOVO Nordisk Foundation and the European Commission, BIOMED 1 Program.

REFERENCES

1. Abe, K.; Fujimura, H.; Nishikawa, Y.; Yorifuji, S.; Mezaki, T.; Hirono, N.; Nishitani, N.; Kameyama, M.: Marked reduction in CSF lactate and pyruvate levels after CoQ therapy in a patient with mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS). Acta Neurol. Scand. 83:356–359; 1991.
2. American Psychiatric Association Task Force on Tardive Dyskinesia: Tardive dyskinesia: A task force report of the American Psychiatric Association. Washington, DC: APA Press; 1992.
3. Andersson, M.; Elmberger, P.G.; Edlund, C.; Kristensson, K.; Dallner, G.: Rates of cholesterol, ubiquinone, dolichol and dolichol-P biosynthesis in rat brain slices. FEBS Lett. 269:15–18; 1990.
4. Andreassen, O. A.; Aamo, T. O.; Jørgensen, H. A.: Inhibition by memantine of the development of persistent oral dyskinesias induced by long-term haloperidol treatment of rats. Br. J. Pharmacol. 119:751–757; 1996.
5. Andreassen, O. A.; Ferrante, R. J.; Beal, M. F.; Jørgensen, H. A.: Oral dyskinesias and striatal lesions in rats after co-treatment

with haloperidol and 3-nitropropionic acid. Neuroscience 87:639–648; 1998.
6. Andreassen, O. A.; Jørgensen, H. A.: GM1 ganglioside attenuates the development of vacuous chewing movements induced by long-term haloperidol treatment of rats. Psychopharmacology (Berlin) 116:517–522; 1994.
7. Andreassen, O. A.; Jørgensen H. A.: The mitochondrial toxin 3-nitropropionic acid induces vacuous chewing movements in rats. Implications for tardive dyskinesia? Psychopharmacology (Berlin) 119:474–476; 1995.
8. Battino, M.; Bertoli, E.; Formiggini, G.; Sassi, S.; Sorini, A.; Villa, R. F.; Lenaz, G.: Structural and functional aspects of the respiratory chain of synaptic and nonsynaptic mitochondria derived from selected brain regions. J. Bioenerg. Biomembr. 23:345–63; 1991.
9. Beal, M. F.; Matthews, R. T.; Tieleman, A.; Shults, C. W.: Coenzyme Q10 attenuates the 1-methyl-4-phenyl-1,2,3,tetrahydropyridine (MPTP) induced loss of striatal dopamine and dopaminergic axons in aged mice. Brain. Res. 783:109–114; 1998.
10. Beal, M. F.; Henshaw, D. R.; Jenkins, B. G.; Rosen, B. R.; Schulz, J. B.: Coenzyme Q10 and nicotinamide block striatal lesions produced by the mitochondrial toxin malonate. Ann. Neurol. 36:882–888; 1994.
11. Behl, C.; Lezoualch, F.; Widmann, M.; Rupprecht, R.; Holsboer, F.: Oxidative stress-resistant cells are protected against haloperidol toxicity. Brain Res. 717:193–195; 1996.
12. Behl, C.; Rupprecht, R.; Skutella, T.; Holsboer, F.: Haloperidol-induced cell death—Mechanism and protection with vitamin E in vitro. Neuroreport 7:360–364; 1995.
13. Brouillet, E.; Henshaw, D. R.; Schulz, J. B.; Beal, M. F.: Aminooxyacetic acid striatal lesions attenuated by 1,3-butanediol and coenzyme Q10. Neurosci. Lett. 177:58–62; 1994.
14. Burkhardt, C.; Kelly, J. P.; Lim, Y. H.; Filley, C. M.; Parker, W. D., Jr.: Neuroleptic medications inhibit complex I of the electron transport chain. Ann. Neurol. 33:512–517; 1993.
15. Burton, G. W.: Vitamin E: Molecular and biological function. Proc. Nutr. Sci. 53:251–262; 1994.
16. Cadenas, E.: Antioxidant and prooxidant functions of DT-diaphorase in quinone metabolism. Biochem. Pharmacol. 49:127–140; 1995.
17. Cadet, J. L.; Lohr, J. B.; Jeste, D. V.: Free radicals and tardive dyskinesia. Trends. Neurosci. 9:107–108; 1986.
18. Cholerton, S.; Daly, A. K.; Idle, J. R.: The role of individual human cytochromes P450 in drug metabolism and clinical response. Trends Pharmacol. Sci. 13:434–439; 1992.
19. Clow, A.; Jenner, P.; Marsden, S. D.: Changes in dopamine-mediated behaviour during one year's neuroleptic treatment. Eur. J. Pharmacol. 57:365–375; 1979.
20. Coyle, J. T.; Puttfarcken, P.: Oxidative stress, glutamate, and neurodegenerative disorders. Science 262:689–695; 1993.
21. DeKeyser, J.: Excitotoxic mechanisms may be involved in the pathophysiology of tardive dyskinesia. Clin. Neuropharmacol. 14:562–565; 1991.
22. Edlund, C.; Holmberg, K.; Dallner, G.; Norrby, E.; Kristensson, K.: Ubiquinone-10 protects neurons from virus-induced degeneration. J. Neurochem. 63:634–639; 1994.
23. Egan, M. F.; Apud, J.; Wyatt, R. J.: Treatment of tardive dyskinesia. Schizophr. Bull. 23:583–609; 1997.
24. Egan, M. F.; Ferguson, J. N.; Hyde, T. M.: Effects of chronic naloxone administration on vacuous chewing movements and catalepsy in rats treated with long-term haloperidol decanoate. Brain Res. Bull. 38:355–363; 1995.
25. Egan, M. F.; Hurd, Y.; Hyde, T. M.; Weinberger, D. R.; Wyatt, R. J.; Kleinman, J. E.: Alterations in mRNA levels of D2 receptors and neuropeptides in striatonigral and striatopallidal neurons of rats with neuroleptic-induced dyskinesias. Synapse 18:178–189; 1994.
26. Ernster, L.; Dallner, G.: Biochemical, physiological and medical aspects of ubiquinone function. Biochim. Biophys. Acta 1271:195–204; 1995.
27. Favit, A.; Nicoletti, F.; Scapagnini, U.; Canonico, P. L.: Ubiquinone protects cultured neurons against spontaneous and excitotoxin-induced degeneration. J. Cereb. Blood. Flow. Metab. 12:638–645; 1992.
28. Feigin, A.; Kieburtz, K.; Como, P.; Hickey, C.; Claude, K.; Abwender, D.; Zimmerman, C.; Steinberg, K.; Shoulson, I.: Assessment of coenzyme Q10 tolerability in Huntington's disease. Move Disord. 11:321–323; 1996.
29. Fisher, G. R.; Patterson, L. H.; Gutierrez, P. L.: A comparison of free radical formation by quinone antitumour agents in MCF-7 cells and the role of NAD(P)H (quinone-acceptor) oxidoreductase (DT-diaphorase). Chem. Biol. Interact. 88:137–153; 1993.
30. Frei, B.; Kim, M. C.; Ames, B. N.: Ubiquinol-10 is an effective lipid-soluble antioxidant at physiological concentrations. Proc. Natl. Acad. Sci. USA 87:4879–4883; 1990.
31. Goda, S.; Hamada, T.; Ishimoto, S.; Kobayashi, T.; Goto, I.; Kuroiwa, Y.: Clinical improvement after administration of coenzyme Q10 in a patient with mitochondrial encephalomyopathy. J. Neurol. 234:62–63; 1987.
32. Goff, D. C.; Tsai, G.; Beal, M. F.; Coyle, J. T.: Tardive dyskinesia and substrates of energy metabolism. Am. J. Psychiatry 152:1730–1736; 1995.
33. Gunne, L. M.; Andersson, U.; Bondesson, U.; Johansson, P.: Spontaneous chewing movements in rats during acute and chronic antipsychotic drug administration. Pharmacol. Biochem. Behav. 25:897–901; 1986.
34. Ihara, Y.; Namba, R.; Kuroda, S.; Sato, T.; Shirabe, T.: Mitochondrial encephalomyopathy (MELAS): Pathological study and successful therapy with coenzyme Q10 and idebenone. J. Neurol. Sci. 90:263–271; 1989.
35. Jayaraman, J.; Joshi, V. C.; Ramasarma, T.: Some aspects of the metabolism of coenzyme Q in the rat. Biochem. J. 88:369–373; 1963.
36. Kane, J. M.: Tardive dyskinesia: Epidemiological and clinical presentation. In: Bloom, F. E.; Kupfer, D. J., eds. Psychopharmacology: The fourth generation of progress. New York: Raven Press; 1995.
37. Kontush, A.; Hübner, C.; Finckh, B.; Kohlschütter, A.; Beisiegel, U.: Low density lipoprotein oxidizability by copper correlates to its initial ubiquinol-10 and polyunsaturated fatty acid content. FEBS Lett. 341:69–73; 1994.
38. Koroshetz, W. J.; Jenkins, B. G.; Rosen, B. R.; Beal, M. F.: Energy metabolism defects in Huntington's disease and effects of coenzyme Q10. Ann. Neurol. 41:160–165; 1997.
39. Langsjoen, P. H.; Folkers, K.: A six-year clinical study of therapy of cardiomyopathy with coenzyme Q_{10}. Int. J. Tissue React. 12:169–171; 1990.
40. Lohr, J. B.; Kuczenski, R.; Bracha, H. S.; Moir, M.; Jeste, D. V.: Increased indices of free radical activity in the cerebrospinal fluid of patients with tardive dyskinesia. Biol. Psychiatry 28:535–539; 1990.
41. Matthews, R. T.; Yang, L.; Browne, S.; Baik, M.; Beal, M. F.: Coenzyme Q10 administration increases brain mitochondrial concentrations and exerts neuroprotective effects. Proc. Natl. Acad. Sci. USA 95:8892–8897; 1998.
42. McGeer, E. G.; McGeer, P. L.: Duplication of biochemical changes of Huntington's chorea by intrastriatal injections of glutamic and kainic acids. Nature 263:517–519; 1976.
43. Mohr, D.; Bowry, V. W.; Stocker, R.: Dietary supplementation with coenzyme CoQ10 results in increased levels of ubiquinol-10 within circulating lipoproteins and increased resistance of human low-density lipoprotein to the initiation of lipid peroxidation. Biochim. Biophys. Acta 1126:247–254; 1992.
44. Mortensen, S. A.: Perspectives on therapy of cardiovascular diseases with coenzyme Q_{10} (ubiquinone). Clin. Investigat. 71:116–123; 1993.
45. Nakamura, T.; Sanma, H.; Himeno, M.; Kato, K.: Transfer of exogenous coenzyme Q to inner membrane of heart mitochondria in rats. In: Yamamura, Y.; Folkers, K.; Ito, Y., eds. Biochemical and clinical aspects of coenzyme Q10, vol. 2. Amsterdam; Elsevier/North Holland; 1989:3–11.
46. Nishikawa, Y.; Takahashi, M.; Yorifuji, S.; Nakamura, Y.; Ueno, S.; Tarui, S.; Kozuka, T.; Nishimura, T.: Long-term coenzyme Q10 therapy for a mitochondrial encephalomyopathy with cytochrome *c* oxidase deficiency: A 31P NMR study. Neurology 39:399–403; 1989.

47. Ogasahara, S.; Yorifuji, S.; Nishikawa, Y.; Takahashi, M.; Wada, K.; Hazama, T.; Nakamura, Y.; Hashimoto, S.; Kono, N.; Tarui, S.: Improvement of abnormal pyruvate metabolism and cardiac conduction defect with coenzyme Q_{10} in Kearns-Sayre syndrome. Neurology 35:372–377; 1985.
48. Ohhara, H.; Kanaide, H.; Yoshimura, R.; Okada, M.; Nakamura, M.: A protective effect of coenzyme Q10 on ischemia and reperfusion of the isolated perfused rat heart. J. Mol. Cell. Cardiol. 13:65–74; 1981.
49. Packer, L.; Fuchs, J.: Vitamin E in health and disease. New York: Marcel Dekker; 1993.
50. Pall, H. S.; Williams, A. C.; Blake, D. R.; Lunec, J.: Evidence of enhanced lipid peroxidation in the cerebrospinal fluid of patients taking phenothiazines. Lancet 2:596–599; 1987.
51. Podda, M.; Weber, C.; Traber, M. G.; Packer, L.: Simultaneous determination of tissue tocopherols, tocotrienols, ubiquinols and ubiquinones. J. Lipid Res. 37:893–901; 1996.
52. Przyrembel, H.: Therapy of mitochondrial disorders. J. Inherit. Metab. Dis. 10(Suppl. 1):129–146; 1987.
53. Reahal, S.; Wrigglesworth, J.: Tissue concentrations of coenzyme Q10 in the rat following its oral and intraperitoneal administration. J. Drug. Metab. Dispos. 20:423–427; 1992.
54. Schneider, H.; Lemasters, J. J.; Hackenbrock, C. R.: Lateral diffusion of ubiquinone during electron transfer in phospholipid- and ubiquinone-enriched mitochondrial membranes. J. Biol. Chem. 257:10789–10793; 1982.
55. Schulz, J. B.; Matthews, R. T.; Henshaw, D. R.; Beal, M. F.: Neuroprotective strategies for treatment of lesions produced by mitochondrial toxins: Implications for neurodegenerative diseases. Neuroscience 71:1043–1048; 1996.
56. Shigeta, Y.; Izumi, K.; Abe, H.: Hepatic content of coenzyme Q in rats after administration of various coenzyme Q compounds and ^{14}C-labeled coenzyme Q_7. J. Vitaminol. 14:278–281; 1968.
57. Stoessl, A. J.: Effects of ethanol in a putative rodent model of tardive dyskinesia. Pharmacol. Biochem. Behav. 54:541–546; 1996.
58. Tsai, G.; Huang, X.; Tanzi, R. E.; Bush, A. I.; Coyle, J. T.: Neurolepitc redox activity: A mechanism for tardive dyskinesia? Soc. Neurosci. Abstr. 23:1953; 1997.
59. Waddington, J. L.; Cross, A. J.; Gamble, S. J.; Bourne, R. C.: Spontaneous orofacial dyskinesia and dopaminergic function in rats after 6 months of neuroleptic treatment. Science 220:530–532; 1983.
60. Weber, C.; Jakobsen, T. S.; Mortensen, S. A.; Paulsen, G.; Hølmer, G.: Antioxidative effect of dietary coenzyme CoQ10 in human blood plasma. Int. J. Vitam. Nutr. Res. 64:311–315; 1994.
61. Wiss, O.; Gloor, H.: Absorption, distribution, storage, and metabolites of vitamins K and related quinones. Vitamins Horm. 24:575–586; 1966.
62. Zhang, Y.; Turunen, M.; Appelkvist, E.: Restricted uptake of dietary coenzyme Q is in contrast to the unrestricted uptake of a-tocopherol into rat organs and cells. J. Nutr. 126:2089–2097; 1996.
63. Zhang, Y.; Åberg, F.; Appelkvist, E.; Dallner, G.; Ernster, L.: Uptake of dietary coenzyme Q supplement is limited in rats. J. Nutr. 125:446–543; 1995.
64. Åberg, F.; Appelkvist, E.; Dallner, G.; Ernster, L.: Distribution and redox state of ubiquinones in rat and human tissues. Arch. Biochem. Biophys. 295:230–234; 1992.