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Transport of Orally Supplemented CoQ10 in the Body

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Abstract. Oral coenzyme Q10 (CoQ10) supplements are widely used to support mitochondrial function and antioxidant defenses. Although studies have reported potential benefits in selected cardiovascular and neurological conditions, the mechanisms governing absorption and delivery to target tissues remain incompletely understood. This review examines the transport of orally administered CoQ10 from the gastrointestinal tract to the circulation, its distribution among organs, and its potential passage across the blood–brain barrier. It considers the redox forms of CoQ10 during intestinal absorption, the effects of supplement formulation and individual physiology on bioavailability, and the role of circulating lipoproteins in transport. It also discusses experimental models used to investigate tissue uptake and candidate mechanisms of blood–brain barrier transport. Finally, the review identifies questions concerning cellular uptake and intracellular delivery to mitochondria. Distinguishing increased plasma concentrations from effective delivery to tissues and subcellular sites is essential for interpreting supplementation studies. A clearer understanding of these processes could guide the design of formulations and experiments that evaluate both target-tissue exposure and functional responses.

Keywords: coenzyme Q10, oral supplementation, tissue distribution, blood–brain barrier, intracellular trafficking

1. Introduction

CoQ10 is a lipid-soluble compound synthesized endogenously. Its functions include stabilizing the plasma membrane and maintaining its fluidity, protecting cellular components from oxidative stress, and supporting mammalian immune function [1-4]. Its best-known role is as an electron carrier in the mitochondrial respiratory chain [5].

Multiple studies have reported potential benefits of oral CoQ10 supplementation, including improved clinical outcomes in patients with chronic heart failure when CoQ10 is used as an adjunct to standard therapy, as well as increased resistance of low-density lipoproteins to ex vivo lipid peroxidation [6, 7]. Oral CoQ10 has also shown neuroprotective potential in preclinical research, reducing brain oxidative stress and improving cognitive performance in a transgenic mouse model of Alzheimer's disease [8]. Furthermore, a phase 2 randomized, placebo-controlled trial reported slower motor deterioration in patients with multiple-system atrophy receiving high-dose oral ubiquinol, the reduced form of CoQ10 [9].

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Despite the reported benefits of CoQ10 supplementation, the processes by which CoQ10 is transported from its sites of absorption to cardiac cells and neurons remain unclear. Moreover, there is little evidence that CoQ10 can cross the blood–brain barrier (BBB) in mouse models [10]. This gap in our understanding of a widely used supplement warrants further investigation. This review explores the transport of CoQ10 from the intestine to the bloodstream, its distribution from the circulation to organs, and its ability to cross the BBB.

2. Transport of CoQ10 from the intestine to the bloodstream

The human gastrointestinal (GI) tract includes several organs that secrete digestive enzymes. These enzymes break down macromolecules into smaller components for absorption. The chemical environment of the GI tract also facilitates biochemical reactions. Ubiquinone, the oxidized form of CoQ10, contains two carbonyl groups; in ubiquinol, its reduced form, these are replaced by two hydroxyl groups. Differences between these redox forms have prompted debate about their relative bioavailability and the form in which CoQ10 is absorbed. A central question is whether CoQ10 undergoes redox reactions in the GI tract before absorption.

A study in mice suggests that both ubiquinone and ubiquinol reach the small intestine largely in the form in which they were administered [11]. The researchers administered a CoQ10 preparation by oral gavage and measured CoQ10 in the small intestine. The mice were euthanized at 0.5, 1, 2, 4, or 8 hours after administration, and their intestines were washed before the intestinal CoQ10 content was analyzed. The small sample size (n = 3 mice per group) limits the precision of the findings. Although the authors reported that washing the intestines once or twice did not affect the measured CoQ10 content, the influence of washing on the measured redox forms requires consideration. The first author also disclosed employment by the manufacturer that supplied the CoQ10 used in the study. In contrast, a study in dogs reported that ingested ubiquinol was converted to ubiquinone before intestinal absorption [12]. Catheters were inserted into the stomach, small intestine, and distal and proximal lymphatic vessels of six dogs, and samples were collected over 0–420 minutes. The study reported that CoQ10 was absorbed predominantly as ubiquinone and subsequently reduced to ubiquinol in the lymphatic system [12].

To investigate absorption and bioavailability, López-Lluch, et al. [13] compared formulations containing ubiquinone or ubiquinol. Fourteen healthy young adults received formulations containing 100 mg of CoQ10, and plasma CoQ10 concentrations were measured over 48 hours. The researchers found that ubiquinone was generally better absorbed than ubiquinol [13]. However, plasma concentrations varied among participants, suggesting that individual physiological factors also influence absorption. These findings suggest that CoQ10 is absorbed in its oxidized form, ubiquinone. Absorption and bioavailability also depend on the carrier lipids and formulation of the supplement, as well as individual physiology.

Because of their structural and chemical similarities, CoQ10, vitamin E, and cholesterol may share aspects of their absorption mechanisms [14]. Together with other lipid-soluble compounds and dietary fats, CoQ10 is incorporated into chylomicrons and crosses the membranes between the small intestine and the bloodstream by passive diffusion [15]. Chylomicrons enter the lymphatic system, where the CoQ10 they carry is reduced to ubiquinol [12]. They then travel to the liver, where CoQ10 associates with lipoproteins and is transported through the capillaries into the circulation. Although CoQ10 has been proposed to share absorption mechanisms with vitamin E and cholesterol, experimental confirmation of its absorption process is lacking.

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3. Distribution of CoQ10 from the circulation to organs

In the circulation, CoQ10 protects lipoproteins against lipid peroxidation as they travel to different organs [7]. Bentinger, et al. [16] used radiolabeled CoQ10 to investigate its distribution after administration. Healthy rats received an intraperitoneal injection on day 0, and CoQ10-associated radioactivity was subsequently assessed in different organs from days 1 to 15. Blood sampling confirmed uptake into the circulation. Plasma radioactivity declined sharply from approximately 15,000 dpm/mg on day 0 to 1,000 dpm/mg on day 4 [16]. Radiolabeled CoQ10 remained relatively abundant in the liver, spleen, adrenal glands, and ovaries (4,000–15,000 dpm/mg on day 15), whereas the thymus contained approximately 2,000 dpm/mg. Radioactivity in the heart fell to approximately 0 dpm/mg on day 15, despite an initial level similar to that in the thymus (6,000 dpm/mg on day 1). Brain radioactivity remained negligible (<50 dpm/mg) throughout the study [16]. The low tissue availability may reflect the formulation: radiolabeled CoQ10 was dissolved in ethanol and mixed with Intralipid for injection, but ethanol and Intralipid may not be optimal carriers [13]. Nevertheless, Bentinger et al. showed that uptake from the circulation differed among organs [16]. The mechanisms by which circulating CoQ10 enters cells remain incompletely understood.

A subsequent study investigated the effects of continuous dietary supplementation on tissue distribution. Sohal, et al. [17] provided female mice with dietary CoQ10 for 1, 20, or 32 months. This approach involved continuous supplementation over a longer observation period, whereas Bentinger et al. administered a single intraperitoneal injection. Sohal et al. found that tissue CoQ10 increased only in the kidneys, with no increase in the heart, skeletal muscle, or brain [17]. Mitochondrial CoQ10 concentrations varied among tissues and differed from concentrations measured in whole-tissue samples. Mitochondrial concentrations increased significantly in the heart, kidneys, and skeletal muscle after 20 months of supplementation, whereas brain mitochondrial concentrations remained unchanged between 7 and 21 months [17]. Although methodological differences prevent direct comparison, both studies reported low CoQ10 accumulation in the heart, brain, and skeletal muscle after supplementation.

Thus, Bentinger et al. observed negligible brain uptake despite measurable circulating CoQ10. Sohal et al. also found limited brain accumulation after long-term supplementation. These findings, together with other reports of limited brain uptake, raise the question of whether and under what conditions CoQ10 crosses the BBB [18].

4. Does CoQ10 cross the blood–brain barrier

The BBB separates the central nervous system (CNS) from the circulation and helps maintain the environment required for neural function. It comprises endothelial cells connected by tight junctions, with associated pericytes and astrocytes [19]. Pericytes contribute to the maintenance and regulation of BBB integrity, while astrocytes are CNS glial cells that regulate the development of barrier properties in endothelial cells [20, 21]. As a lipophilic compound, CoQ10 has been hypothesized to diffuse passively across the BBB. However, the tight junctions permit passage only of substances with molecular masses of approximately 400–600 Da, whereas the exact mass of CoQ10 is 862.68 Da [22]. Whether CoQ10 crosses the BBB remains unresolved, and much mechanistic research relies on cell models because direct studies in humans are difficult. Oral CoQ10 supplementation at 200 mg/kg for two months increased cerebral cortical CoQ10 concentrations in mice ($p < 0.05$) [10]. The mechanisms responsible for transport from the bloodstream into the brain remain unclear.

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Wainwright, et al. [23] used BBB models to investigate potential CoQ10 transport mechanisms. They established an in vitro model using primary porcine brain endothelial cells (PBECs) co-cultured with astrocytes and assessed transport in both the apical-to-basal (blood-to-brain) and basal-to-apical (brain-to-blood) directions. Preincubation with serum increased CoQ10 transport across the barrier ($p < 0.01$) [23]. A similar effect was observed in a model based on the murine brain endothelial cell line bEnd.3. As discussed above, circulating CoQ10 associates with lipoproteins [7]. To investigate their contribution, the researchers measured CoQ10 in serum lipoprotein fractions before and after supplementation. CoQ10 accumulated predominantly in low-density lipoprotein (LDL; 63.8%) and very-low-density lipoprotein (VLDL; 29.0%) fractions. These results implicate serum lipoproteins as carriers that facilitate CoQ10 transport across the in vitro BBB.

The bEnd.3 model was more permeable than the PBEC model, with transendothelial electrical resistance (TEER) values of approximately 41 and 946 $\Omega \cdot cm^2$, respectively. However, the bEnd.3 model was more reproducible and amenable to experimental manipulation. Wainwright et al. therefore used bEnd.3 cells to examine several transport systems: scavenger receptor class B type 1 (SR-B1), a high-density lipoprotein receptor involved in cholesterol transport [24]; the receptor for advanced glycation end products (RAGE); and the LDL receptor and related receptors (LDLR family) [23]. Using BLT-1, FPS-ZM1, and receptor-associated protein (RAP) as inhibitors of these respective systems, the researchers found that SR-B1 and RAGE were required for CoQ10 uptake toward the brain side, whereas LDLR-family activity contributed to transport toward the blood side [23]. Under control conditions, there was no net transport across the barrier. Inhibition of CoQ10 biosynthesis shifted transport toward the basal compartment. Deficiency was induced using para-aminobenzoic acid (pABA), which inhibits Coq2p, an enzyme involved in CoQ10 biosynthesis [25]. Following pABA treatment, complex I activity ($p < 0.001$), combined complex II–III activity ($p < 0.001$), and complex IV activity ($p < 0.05$) were reduced. Thus, mitochondrial respiratory dysfunction in BBB endothelial cells was accompanied by increased CoQ10 transport from the blood side toward the brain side [23]. This observation is consistent with a report of two siblings with severe encephalomyopathy and renal failure, in whom widespread CoQ10 deficiency was associated with impaired respiratory-chain function [26].

Several studies have proposed CoQ10 supplementation for neurodegenerative diseases and reported increased serum CoQ10 concentrations after treatment [27]. Clinical trials have shown beneficial effects in these diseases, particularly in conditions associated with CoQ10 deficiency [27]. The findings of Wainwright et al. offer a possible mechanistic explanation by showing that impaired mitochondrial function in BBB endothelial cells can favor transport toward the brain side.

5. Conclusion and future directions

This review examines the transport of CoQ10 after oral supplementation. CoQ10 reaches the small intestine, is absorbed as ubiquinone and incorporated into chylomicrons, and is reduced to ubiquinol in the lymphatic system. Absorption and bioavailability depend on supplement formulation and carrier composition. In the circulation, CoQ10 associates with lipoproteins. Tissue uptake is selective, with limited accumulation in the heart, brain, and skeletal muscle. The ability of CoQ10 to cross the BBB remains an important question. SR-B1, RAGE, and LDLR-family receptors have been proposed as candidate mediators of transport across the barrier. Although no net transport was observed under control conditions, mitochondrial dysfunction in BBB endothelial cells favored transport toward the brain side. Clinical trials have reported benefits in patients with

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neurodegenerative disease and mitochondrial dysfunction, particularly those with CoQ10 deficiency, but the transport mechanisms remain understudied.

Future studies should investigate the mechanisms of CoQ10 transport across the BBB in greater detail. One approach would be to monitor CoQ10 in the brain and plasma of living model organisms after oral supplementation. Radiolabeling, as used by Bentinger et al. to study tissue distribution, could provide a noninvasive means of monitoring CoQ10 over time [16]. Emerging approaches, such as nanoelectrode arrays, may also offer ways to measure its concentration and distribution in real time. Another important question is how CoQ10 is trafficked within cells. After reaching a tissue, CoQ10 must enter cells and reach appropriate subcellular sites to support mitochondrial function and antioxidant defense. Candidate mechanisms include the endoplasmic reticulum–mitochondria encounter structure (ERMES), VPS13-family proteins, and related pathways that require further investigation [14, 28-30].

Understanding CoQ10 transport is essential for interpreting both bioavailability and therapeutic potential. An increase in circulating CoQ10 after oral supplementation does not necessarily indicate effective delivery to target tissues, cells, or subcellular sites such as mitochondria. Defining the mechanisms of intestinal absorption, lipoprotein-associated transport, tissue uptake, BBB passage, and intracellular trafficking will help distinguish systemic exposure from biologically effective delivery. This knowledge may also help explain variable responses to supplementation across tissues, diseases, and clinical studies. Identifying rate-limiting transport steps could guide the development of formulations that improve target-tissue exposure. Future studies should therefore evaluate the entire delivery pathway, from oral administration and circulation to tissue accumulation, cellular uptake, subcellular localization, and functional responses.

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