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Review

COQ4 and COQ8A Primary Deficiencies: A Review of Proposed Therapeutic Strategies

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Abstract

In this article we have reviewed potential therapeutic strategies relating to two of the primary coenzyme Q10 (CoQ10) deficiencies, COQ4 and COQ8A; these disorders have been grouped together because of their complimentary roles in stabilising the CoQ10 enzyme complex, Complex Q, as well as the difficulty in treating either of these disorders using conventional oral supplementation, as exemplified by two previously unreported case histories. Alternative strategies reviewed include methods to potentially improve blood-brain barrier access, including the identification of suitable inhibitors or activators of LRP1 or SRB1 transporters respectively. Other potential therapeutic strategies include the potential stabilisation of Complex Q using agents such as cardiolipin, targeted gene therapy using CRISPR/Cas9 gene-editing or AAV vector gene delivery, or mitochondrial transplantation. All of the strategies outlined above are at an early preclinical stage with regard to their potential application in primary CoQ10 deficiency, and remain areas for ongoing research.

Keywords: coenzyme Q10; COQ4 deficiency; COQ8A deficiency; blood-brain barrier access; targeted gene therapy; mitochondrial transplantation

1. Introduction

Coenzyme Q10 (CoQ10) has a number of key functions in supporting normal cell metabolism; principally, its role is in cellular energy supply/ATP synthesis via mitochondrial oxidative phosphorylation, but it also acts as a major endogenously synthesised lipid-soluble antioxidant, protecting cellular/sub-cellular organelle membranes from free radical-induced oxidative damage. Within the mitochondrial electron transport chain, CoQ10 accepts electrons from Complex I and Complex II, moving through the mitochondrial lipid bilayer to deliver these electrons to Complex III. This continuous electron flow drives protons out of the mitochondrial matrix, generating the electrochemical gradient required by ATP synthase to generate ATP. CoQ10 exerts its full antioxidant capacity when in the reduced form of ubiquinol; in addition to preventing lipid peroxidation within membranes, ubiquinol also helps regenerate other antioxidants such as vitamins C and E. CoQ10 also has important roles in the metabolism of lysosomes, sulphides, amino acids, pyrimidine, and cholesterol, as well as a role in directly mediating the expression of more than one hundred genes, including those involved in the inflammatory process. CoQ10 is involved in lysosomal acidification, transporting protons into these organelles. CoQ10 acts as an electron acceptor for dihydroorotate dehydrogenase, a key enzyme required for the biosynthesis of pyrimidines; CoQ10 also serves as a cofactor for enzymes involved in

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amino acid catabolism (proline and choline dehydrogenases) and sulphide detoxification (sulphide quinone oxidoreductase) [1].

Given its key role in normal cellular metabolism, it is unsurprising that deficiency of CoQ10 has been implicated in the pathogenesis of a number of disorders. Randomised controlled clinical trials have reported significant symptomatic benefit in conditions such as heart failure following CoQ10 supplementation [2]. However, although CoQ10 deficiency and mitochondrial dysfunction have been reported in a number of neurological disorders (Table 1), the outcomes of clinical studies supplementing CoQ10 in such disorders have in general been disappointing, and this in turn is a likely consequence of the difficulty of exogenous CoQ10 in accessing the human blood brain barrier (BBB) [3].

Table 1. Examples of neurological disorders in which mitochondrial dysfunction and CoQ10 deficiency have been identified.

Disorder	Mitochondrial Dysfunction References	CoQ10 Deficiency	CoQ10 Deficiency References
Parkinson's disease	Usha-Kiran et al. [4]	CNS tissues (substantia nigra, frontal cortex) and peripheral tissues (platelets, lymphocytes, fibroblasts)	Shults et al. [5]; Hargreaves et al. [6]
Alzheimer's disease	Bisht et al. [7]	Serum	Chang et al. [8]
Huntington's disease	Kuwar et al. [9]	Serum	Andrich et al. [10]
Amyotrophic lateral sclerosis	Mitsumoto et al. [11]	Increased ratio of oxidised to reduced forms in plasma	Sohmiya et al. [12]; Wang et al. [13]
Multiple sclerosis	Navazi et al. [14]	Serum	Moccia et al. [15]

With regard to COQ4/COQ8A deficiencies (particularly those manifestations affecting neurological function), the deficiency of CoQ10 is broadly divided into two types, primary and secondary. Primary CoQ10 deficiency results from mutations in genes involved in the CoQ10 biosynthetic pathway, with secondary CoQ10 deficiency resulting from causes other than the former (e.g., unrelated genetic conditions, environmental factors, effect of pharmacological agents, ageing) [16]. In humans, at least 10 genes (designated as *PDSS1/PDSS2* to *COQ10*) are required for the biosynthesis of functional CoQ10, a mutation in any one of which can result in a deficit in CoQ10 status.

The biosynthesis of CoQ10 is a complex, multistep process that takes place in various sub-cellular locations. The polyisoprenoid tail is synthesised in the cytosol via the mevalonate pathway, with attachment to the benzoquinone ring taking place within the mitochondria. The ring structure is then further modified via hydroxylation, methylation, and decarboxylation by a set of enzymes grouped in a complex (Complex Q in humans; Q syndrome in yeast; Figure 1). Complex Q comprises proteins COQ3–COQ9, together with various cofactors, and is associated with the matrix face of the inner mitochondrial membrane (Figure 1); it organises the individual synthetic enzymes in a way that maximises synthetic efficiency while preventing the escape of non-functional intermediate metabolites [17].

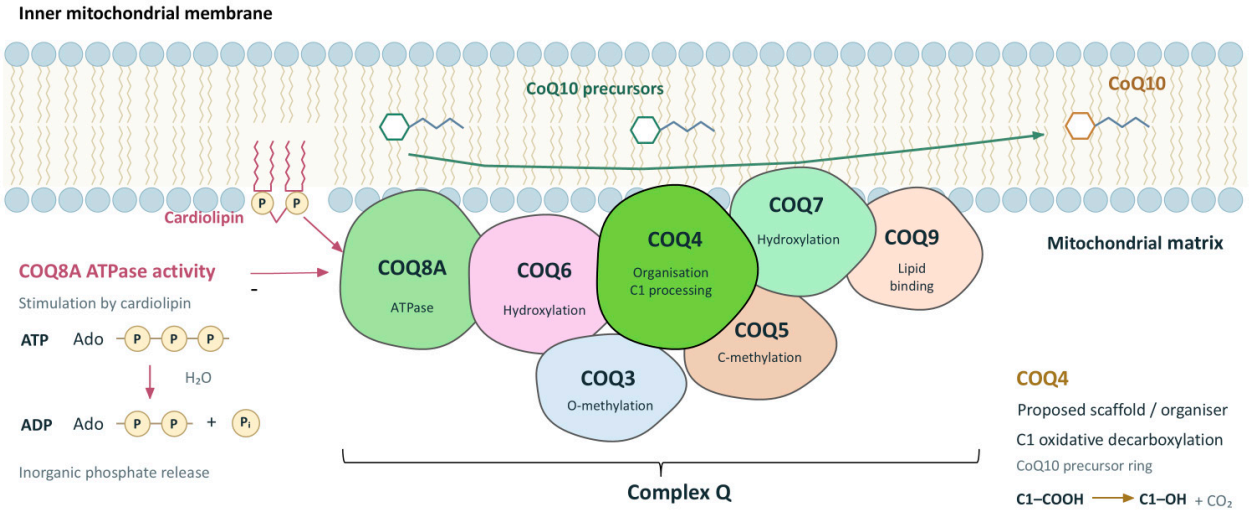

Figure 1. Organisation and regulation of human Complex Q. Selected COQ proteins associate with the matrix face of the inner mitochondrial membrane. COQ3 and COQ5 catalyse O- and C-methylation, respectively, while COQ6 and COQ7 participate in hydroxylation. COQ9 binds lipids and supports the COQ7-associated biosynthetic machinery. COQ4 has a proposed scaffold/organiser role and contributes to oxidative decarboxylation at C1 of CoQ10 precursors. The C1–COOH to C1–OH + CO_2 inset is a schematic net transformation, not a fully balanced reaction or detailed chemical structure. COQ8A is depicted as an ATPase regulator. Cardiolipin stimulates COQ8 membrane interaction and ATPase activity. The ATP diagram shows phosphate groups and inorganic phosphate release, not phosphotransfer to another protein. Ado, adenosine; P, schematic phosphate group; Pi, inorganic phosphate. The cardiolipin icon depicts two phosphate groups and four acyl tails, but is not an atom-resolved structure. The green arrow depicts net CoQ biosynthesis rather than individual reaction order. No specific protein phosphorylation sites are asserted. COQ8B and upstream/peripheral proteins are omitted to focus on the COQ4/COQ8A review. Positions, shapes, contacts and stoichiometry do not depict an experimentally resolved human holocomplex.

The authors' attention was focussed on COQ4 and COQ8A deficiencies following a request for assistance from the parents of two unrelated children with primary CoQ10 deficiency, The first patient was diagnosed in infancy with neurological problems associated with COQ4 deficiency linked to c.469C>A and c.718C>T variants. Long term supplementation with CoQ10 provided no significant benefit for the patient's neurological symptoms. This case history highlights several issues. Firstly, the bioavailability of CoQ10 supplements can vary considerably; since the levels of CoQ10 in blood or tissue biopsy were not measured during supplementation, it is uncertain how much of the supplemented CoQ10 reached the blood circulation. Secondly, there is the further issue of the difficulty of circulatory CoQ10 accessing the BBB, and whether any of the supplemented CoQ10 reached brain tissue. Finally, there is the issue of the specific genetic variant affecting this patient, which is known to be refractory to CoQ10 supplementation. These issues collectively suggested that alternative therapeutic strategies were required for this patent.

The second patient was diagnosed at age 13 with neurological symptoms associated with COQ8A deficiency resulting from compound heterozygous variants c1015G>A (p.Ala339Thr) and c.1665G>A (p.Met555Ile), While there was some symptomatic improvement in this patient following CoQ10 supplementation, there was clearly scope for additional treatment strategies In this article, we have therefore reviewed potential therapeutic strategies relating to the primary CoQ10 deficiencies COQ4 and COQ8A; in addition to the rationale for investigation noted above, these disorders have been grouped together because of their complimentary roles in stabilising Complex Q, as well as the difficulty in treating either of these disorders. It should be noted that standard clinical practice for the

treatment of these disorders is limited to oral supplementation with CoQ10; none of the potential alternative therapeutic strategies described in subsequent sections of this article have to date been evaluated in human subjects.

2. COQ4 Deficiency

Primary CoQ10 Deficiency-7 (COQ10D7) is an autosomal recessive disorder resulting from mutations in the COQ4 gene. The COQ4 gene is located on chromosome 9 and comprises seven exons. The COQ4 gene encodes a multienzyme complex organisation/stabilisation protein, the so-called ubiquinone biosynthesis protein COQ4 homolog, a 265-amino acid protein localised to the matrix side of the mitochondrial inner membrane. COQ4 is thought to function as a scaffold or organizer protein that anchors Complex Q to the inner mitochondrial membrane, enabling ring modifications to CoQ10 precursors in the CoQ10 biosynthetic pathway, with the C-terminus of COQ4 being essential for maintaining this function. In addition to this structural role, there is evidence that COQ4 may also have an enzymic function, catalysing the decarboxylation and hydroxylation of CoQ10 precursors at position C1 [18].

As with other *COQ* mutations, the severity of disease depends on the location of the mutation. In general terms, mutations in exons 1–4 are associated with less life-threating presentations, a late onset, responsiveness to CoQ10 therapy, and a relatively long lifespan. In contrast, pathogenic mutations in exons 5–7 are associated with an early onset (encephalopathy, epilepsy, or cardiomyopathy), unresponsiveness to CoQ10 therapy, and early death. Exons 1–4 encode the N-terminus of the COQ4 protein, which includes the vital mitochondrial targeting sequence that directs the protein to where it is needed within the cell. Because pathogenic variants in exons 1–4 are typically associated with residual protein function, patients usually respond well to high-dose oral CoQ10 supplementation. Exons 5–7 encode the C-terminus of the COQ4 protein, with mutations in exons 5–7 resulting in a near total loss of the COQ4 protein structure. However, it should be noted that exon location alone can be insufficient to predict residual protein activity or treatment response in individuals with *COQ4* gene variants. For example, a missense mutation in exons 1–4 may allow the protein to retain partial function, whereas a nonsense mutation in the same region could cause a near-total loss of the proteinThe outcome of CoQ10 supplementation in COQ4 deficient patients with various mutations in exons 1–4 and 5–7 has been summarised in the review by Xie et al. [19].

Even with sufficient exogenous CoQ10, the mitochondrial electron transport chain may continue to fail if the structural core of Complex Q is missing or severely deformed. In addition to its role in CoQ10 biosynthesis, Complex Q supports the integrity of the inner mitochondrial membrane [20]. It is therefore hypothesised that transfer of exogenous CoQ10 across the mitochondrial membrane and subsequent access to the electron transport chain is compromised. Exogenous CoQ10 must cross the mitochondrial membrane to access the electron transport chain, a process that is highly inefficient in the face of structural defects resulting from dysfunctional Complex Q. In addition, Complexes I, II, and III rely on specific spatial interactions within the lipid bilayer to transfer electrons. A deformed or absent structural core halts electron channelling, causing severe localized oxidative stress and impaired ATP production.

3. COQ8A Deficiency

Primary CoQ10 deficiency deficiency-4 (COQ10D4) is an autosomal recessive disorder caused by mutations in the *COQ8A* gene (previously *ADCK3*).

The *COQ8A* gene is located on chromosome 1 and comprises 18 exons. The *COQ8A* gene encodes an atypical protein kinase, which acts as a crucial ATPase and regulator

Complex Q, and its loss disrupts the structural integrity and enzymatic activity of the synthome. Patients with mutations in this gene typically develop childhood-onset cerebellar atrophy and ataxia, and have a decreased CoQ10 content in their muscle, fibroblast, and lymphoblast cells. Some individuals experience severe, life-threatening symptoms in infancy (e.g., epileptic encephalopathy or heart failure), while others may develop milder forms that manifest later in childhood or adulthood with movement disorders and muscle weakness. CoQ10 deficiency impairs the mitochondrial electron transport chain and ATP production, resulting in energy failure in the brain, particularly in the cerebellum. The cerebellum, which is responsible for coordination, is highly energy-dependent. The lack of CoQ10 leads to dysfunction of Purkinje cells (the main neurons in the cerebellar cortex), causing progressive cerebellar ataxia. Oral CoQ10 supplementation is the primary treatment. In some patients, particularly those with later-onset or milder mutations, high-dose CoQ10 therapy has been shown to stabilize the condition and significantly improve neurological symptoms. The ataxic forms of this disorder are known for being particularly unresponsive to CoQ10 treatment [17].

4. CoQ10 Supplementation

As noted above, oral supplementation with CoQ10 is the principal therapeutic strategy for patients with COQ4 or COQ8A deficiencies. However, there are several issues relating to CoQ10 supplementation that need to be addressed relating to supplement quality and bioavailability, and whether CoQ10 can access the human BBB; these issues are addressed in the following section.

CoQ10 supplement quality and bioavailability: The manufacture of medicinal products and nutritional supplements is subject to different regulations. Medicinal products must be manufactured to exacting standards, relating both to the various steps in the manufacturing process, and the characteristics of the finished product, as well as other factors such as subsequent product distribution- this is known as manufacture to pharmaceutical standards. Nutritional supplements need only be manufactured to comply with general food safety regulations, which are not as strict as pharmaceutical standards. The best CoQ10 supplements in terms of product quality are therefore those manufactured to pharmaceutical standards.

Bioavailability is defined as the proportion of an ingested substance that reaches the blood circulation following absorption from the digestive tract. Because of its chemical structure and extreme hydrophobicity, the bioavailability of supplemental CoQ10 is low, of the order of 10% even for the very best supplements. The formulation of supplemental CoQ10 is of key importance in optimising bioavailability. In this regard, the clinical study by Lopez-Lluch and colleagues [21] is of particular note. In this study, the bioavailability of seven CoQ10 supplements differing in formulation (CoQ10 crystal dispersion status, type of carrier oil, composition of other excipients, and CoQ10 oxidation state) were administered in a single 100 mg dose to the same series of 14 healthy individuals, using a crossover/washout protocol. Bioavailability of the different formulations was quantified as the area under the curve (AUC) at 48 h. Optimum bioavailability was noted for a CoQ10 supplement in ubiquinone form that had been subject to a patented thermal CoQ10 crystal dispersion process. The CoQ10 raw material supplied to supplement manufacturers comes in the form of polymorphic crystals, which cannot be absorbed from the digestive tract. The CoQ10 crystals must therefore be dissociated first into individual CoQ10 molecules, which should remain fully dissociated throughout the shelf life of the supplement.

CoQ10 access across the human BBB: Symptomatic improvement following supplementation with CoQ10 has been reported in some types of primary CoQ10 deficiency, notably those involving peripheral tissues such as muscle or kidneys, but has been less

successful in neurological disorders; this, in turn, may be linked to difficulty CoQ10 has in crossing the human BBB. To date, no clinical studies have been published in which orally administered CoQ10 was shown directly to cross the BBB and access human brain. Such studies would involve, for example, the use of the imaging of radiolabelled CoQ10, or the analysis of tissue biopsy samples, which for obvious ethical reasons, would not be possible. Wainwright et al. [22] used a 2D porcine endothelial monolayer cell BBB model system to investigate access by CoQ10. In this model system, CoQ10 was transported in the apical to basal direction (i.e., blood to brain side) via lipoprotein-associated transcytosis, interacting with the SR-B1 (Scavenger Receptor) and RAGE (Receptor for Advanced Glycation End products) receptors. However, it is simultaneously effluxed back to the blood side via the LDLR (Low Density Lipoprotein Receptor) transporter, leading to no net accumulation of CoQ10 in the brain.

5. Alternative Therapeutic Strategies

Improved BBB access: There are a number of methods by which access of CoQ10 across the BBB into human brain could potentially be improved, including intranasal administration, inhibition of LRP1, activation of SRB1, the use of lipid based nanocarriers, and intrastriatal administration. The potential for intranasal administration of CoQ10 to improve brain access by bypassing the BBB has been reviewed [3]. Briefly, intranasal drug delivery provides a mechanism by which drugs can be delivered directly into the brain, via transport along the olfactory and trigeminal nerves, bypassing the BBB. While this route has been used for the administration of several prescription type medicinal products relevant to the treatment of CNS disorders, to date there have been no clinical studies assessing intranasal administration of CoQ10 to human subjects or indeed animal studies utilized to evaluate this tentative delivery system.

The role of low density lipoprotein receptor-related protein 1 (LRP1) in the BBB preventing access of CoQ10 into the brain has been noted in Section 4 of this article, suggesting inhibition of LRP1 could improve CoQ10 brain access. Because LRP1 has a number of roles in cell metabolism, including lipid and glucose homeostasis, energy balance and signaling [23], generalised inhibition using inhibitors such as RAP (which blocks the binding of virtually all known LRP1 ligands) is not recommended. The objective would therefore be to identify inhibitors that could selectively block the interaction of CoQ10 with LRP1, and this is an area requiring further research. It is of note that although inhibition of LRP1 is of relevance to the treatment of inflammatory disorders and cancer, to date there are no LRP1 inhibitors that have been given regulatory approval as medicinal drugs.

Scavenger receptor class B type 1 (SRB1) facilitates the transport of lipids (particularly HDL- and LDL lipoproteins) from the blood across the epithelial cells of the BBB via transcytosis [24]. SRB1 acts as a receptor that binds lipoproteins at the luminal (blood) surface, initiates their internalization, and moves them through the cell for release at the basolateral (brain) side. Activation of SRB1 is a promising strategy to improve the delivery of therapeutic agents across the BBB by exploiting its natural role in transporting lipoproteins. Engineering drug carrying nanoparticles (linked to ApoA1 or ApoE3 to enhance targeting) to mimic natural HDL particles allows them to bind directly to SR-B1, facilitating transport across the BBB. The protein corona of these nanoparticles (specifically the ApoA1 or ApoE3 ligands) acts as a homing device. When circulating through the brain's microvasculature, ApoE3 primarily binds to the Low-Density Lipoprotein Receptor (LDLR), while ApoA1 demonstrates a strong affinity for Scavenger Receptor Class B Type 1 (SR-B1). The interaction between these apolipoproteins and their respective endothelial receptors on brain microvascular endothelial cells triggers receptor-mediated endocytosis. The nanoparticles are internalized into vesicles and shuttled across the endothelial cyto-

plasm without disrupting the tight junctions of the BBB. Once transcytosed across the BBB, the nanoparticles can release their therapeutic cargo directly into the brain parenchyma, targeting neurons [25]. Because SRB1 is involved in many, often opposing, physiological processes such as lipid transport or inflammation regulation, specific targeted activation is essential to avoid unwanted side effects, such as disrupted lipid homeostasis, macrophage over-activation, or enhanced viral entry [24].

Lipid based nanocarriers (LBNs) are nanosystems (typically 10–1000 nm) designed to facilitate the delivery of encapsulated drugs, and comprise categories including liposomes, solid lipid nanoparticles, nanoemulsions, niosomes, proniosomes and cubosomes. LBNs are designed to improve the bioavailability of hydrophobic drugs, being able to carry a high payload of active ingredients, while their nanoscale size allows for favourable interactions with biological membranes, including the BBB. The lipid composition of LBNs allows them to interact with and traverse the hydrophobic barrier of the BBB via endocytosis, transcytosis, and receptor-mediated mechanisms.

A number of preclinical studies in animals have shown LBNs can significantly improve the delivery of CoQ10 across the BBB. For example, administration of CoQ10 via solid lipid nanoparticles improved access of CoQ10 across the BBB in rats [26]. Similarly, a CoQ10 liposomal nanoparticle formulation was reported to improve the ability of CoQ10 to cross the BBB in mice [27]. However, to date, there have been no published clinical studies that have directly demonstrated that LPNs enable CoQ10 to cross the human BBB, and this remains an area for further research.

Intrastriatal drug administration is a highly specialized invasive neurosurgical technique used to deliver therapeutic agents directly into the striatum of the brain, primarily to bypass the BBB for treating neurodegenerative disorders, in particular Parkinson's disease. Delivery techniques include stereotaxic injection, in which an agent is injected directly into the target area, continued infusion via implanted catheters, and convection enhanced delivery, in which a pressure gradient is used to push agents through the brain's extracellular space, allowing for broader and more even distribution compared to simple diffusion. While intrastriatal administration has been more widely studied in preclinical models, clinical studies in Parkinson's disease patients using this technique include the intrastriatal infusion of viral vectors to introduce genes that either produce dopamine-synthesizing enzymes, and the administration of glial cell line derived neurotrophic factor (GDNF). In each case, the objective of these treatments was to deliver genes that produce dopamine-synthesizing enzymes, neurotrophic factors to stimulate dopaminergic neuronal survival, or introduce dopamine producing neurons, respectively [28–30]. Specifically with regard to CoQ10, intrastriatal administration in a rat model of Parkinson's disease was reported to protect dopaminergic neurons from degeneration, at a very much lower dose (by a factor of 17,000) than that required for an oral dose to achieve a comparable effect [31]. However, to date there have been no reported clinical studies assessing the efficacy of the intrastriatal administration of CoQ10 in human subjects.

Bypass strategies: As noted above, a major problem in treating primary CoQ10 deficiencies is the poor bioavailability of supplemental CoQ10, both in terms of lack of absorption from the digestive tract and inability to cross the human BBB. Bypass strategies aim to circumvent this problem by using more bioavailable precursor analogues that can enter the cell and be incorporated into the CoQ10 synthesis pathway downstream of the affected enzyme, examples being 4-hydroxybenzoic acid, 2,4-dihydroxybenzoic acid or vanillic acid, which in contrast to CoQ10, are small, water-soluble molecules that can provide chemical groups lacking due to defects in specific enzymes. The majority of the studies to date which have assessed bypass strategies for the treatment of primary CoQ10 deficiency have been carried out using animal models or cultured cells from CoQ10-deficient patients; however,

such studies have identified beneficial outcomes based on supplementation with 4-HB or its analogues in COQ2, COQ6, COQ7, and COQ9 deficiencies [32].

In mouse models of COQ2 deficiency, prenatal and continuous 4-HB supplementation rescued perinatal lethality, corrected cardiac insufficiency and prevented fatal neurodevelopmental deterioration. In patients with COQ2 deficiency, oral 4-HB induced rapid remission of renal symptoms (proteinuria), normalized renal hyperfiltration, and yielded significant improvements in motor skills, cognitive alertness, and language acquisition. In animal models of COQ7 deficiency, administration of 2,4-dihydroxybenzoic acid (also known as β-resorcylic acid) enabled bypass of the C6-hydroxylation step governed by COQ7, successfully increasing tissue CoQ10 levels, restoring mitochondrial respiration and significantly extended lifespan. Administration of 2,4-dihydroxybenzoic acid has similarly shown promise as a bypass mechanism in COQ9-deficient models, correcting mitochondrial proteome perturbations and improving cellular bioenergetics [32].

However, in a COQ4-deficient cell line, supplementation with 2,4-DHB or vanillic acid failed to alleviate COQ4 deficiency. This may be mainly because of the structural function of COQ4 rather than its decarboxylase activity, which is required to stabilise the CoQ multienzyme complex. Because COQ4 provides structural integrity to the complex, its absence prevents the proper assembly of the biosynthetic machinery. Consequently, providing unnatural head group precursors, such as 2,4-DHB or vanillic acid, cannot bypass the structural failure of the complex, making them ineffective treatments for *COQ4* defects [32].

Administration of CoQ4: Research in cellular models indicates that CoQ4 itself acts as a functional substitute for CoQ10 and operates effectively at much lower doses, although whether CoQ4 can access the human BBB has still to be determined [33].

Stabilisation of Complex Q: As noted above, both COQ4 and COQ8A deficiencies are associated with destabilisation of Complex Q, resulting in reduced synthesis of CoQ10 and depleted ATP generation. Several substances have been identified with the potential to help stabilise Complex Q, notably cardiolipin and 2-propylphenol. Cardiolipin is a phospholipid present in the inner mitochondrial membrane, which is able to bind to and activate the ATPase activity of COQ8A. Once activated by cardiolipin, COQ8A utilizes its enhanced ATPase activity to recharge its nucleotide-binding pocket. This process stabilizes the multiprotein Complex Q. While direct supplementation of cardiolipin to patients is not currently a established treatment, the scientific evidence suggests that enhancing cardiolipin levels or maintaining its integrity within the mitochondrial membrane could aid in managing COQ8A deficiency. Similarly, the compounds 2-propylphenol and 2-allylphenol have been identified as activators of COQ8A via activation of ATPase activity, with the potential to help stabilise complex Q and thus benefit COQ8A deficiency. It is of note that if Complex Q is defective, the mitochondrial electron transport chain may still fail, even in the presence of supplementary CoQ10; this may result from destabilisation of components such as Complex I or Complex III, and/or the accumulation of toxic CoQ10 intermediate metabolites [34,35].

Gene therapy based strategies: Another novel treatment strategy for COQ4 deficiency is targeted gene therapy. In principal, inserting a functional copy of the *COQ4* gene into patient cells could restore the ability to produce CoQ10, stabilizing mitochondrial function and preventing neurological or cardiac damage. Because *COQ4* deficiency is a monogenic (single-gene) disorder, it is a viable long-term target for CRISPR gene therapy. With the development of induced pluripotent stem cells and gene editing technology, in vitro and in vivo disease models can be established more readily to advance the development of gene therapy. Researchers have successfully used CRISPR/Cas9 gene-editing technology to correct disease-causing *COQ4* mutations in human induced pluripotent stem cells. Romero-Moya et al. [36] described the rescue of mitochondrial and skeletal muscle impairment

in iPSCs with a *COQ4* c.483G > C variant. Editing the mutated *COQ4* gene back to the normal sequence has been shown to fully reverse cellular CoQ10 deficiency and restore mitochondrial function. Stem cells have also been used to create COQ4 deficient models, enabling the study of how the mutation damages nerve and muscle cells, and to test potential therapies. Getting the CRISPR/Cas9 machinery safely and effectively specifically into brain as a target tissues in a living patient remains a significant scientific hurdle. Unlike sickle cell disease, where CRISPR therapy has advanced to clinical application, the use of CRISPR to treat *COQ4* in living humans is still in the early research phase, and currently there are no approved gene therapies for this condition.

In addition to the above, another therapeutic option is adeno-associated virus (AAV) vectors to deliver functional copies of the human COQ4 gene to affected tissues. AAV has a good safety profile, being naturally non-pathogenic, causing negligible immune responses, and generally remaining as an episome without integrating into the host's chromosomal DNA. The AAV genome has a strict packaging capacity of approximately 4.7kb. Because the human *COQ4* cDNA is small, it easily fits within the AAV vector payload limit, alongside necessary regulatory elements. There some thirteen natural serotypes (and engineered variants) with specific tropisms. For COQ4-related disease, neurotropic or myotropic AAV capsids could be selected to target CNS (AAV2) or skeletal/cardiac muscle (AAV1) tissues directly. A single administration yields long-term, sustained transgene expression in non-dividing cells like neurons and mature muscle fibers. Thus in practice the viral genome would be hollowed out and replaced with functional human *COQ4* cDNA and a suitable promoter. The AAV vector then binds to specific cell-surface receptors and is internalized, traveling to the nucleus. Within the nucleus, the viral DNA forms a stable episome, allowing the cell's machinery to transcribe and translate the functional COQ4 protein, thereby restoring the structural stability of Complex Q and correcting electron transport chain dysfunction [37,38].

Mitochondrial transplantation: Mitochondrial transplantation has the potential to benefit patients with rare genetic disorders. As an example, a compassionate use clinical study in six children with Pearson's syndrome or Kearns-Sayre syndrome found transplantation of maternal mitochondria to be safe and effective in promoting promising early symptomatic improvements in these children with single large scale mitochondrial DNA deletion syndromes. In this so-called mitochondrial augmentation therapy, hematopoietic stem cells were harvested from the children, augmented with healthy functional mitochondria donated by their mothers, and the augmented stem cells infused back into the children. No serious adverse effects were noted resulting from introduction of the maternal mitochondria; the procedure resulted in an increase in total mitochondrial DNA content with corresponding clinical improvement, including gains in body weight and improvements in quality of life and aerobic function [39].

Mitochondrial transplantation has theoretical potential to benefit patients with COQ4 or COQ8A deficiency, but there are several potential problems that would need to be addressed. Because COQ4 or COQ8A deficiency typically involves neurological dysfunction, the effective delivery of transplanted mitochondria across the human BBB remains a major obstacle. Similarly, because COQ4 or COQ8A deficiency results from a mutation in nuclear, rather than mitochondrial DNA, transplanting healthy mitochondria does not address the underlying genetic error. Over time, the host cell's dysfunctional environment will stop producing the necessary structural proteins to support CoQ10 synthesis within the newly transplanted mitochondria, potentially limiting how long such treatment remains effective; thus, patients would likely require lifelong repeated administration of transplanted mitochondria to maintain the therapeutic benefit. Notwithstanding the above issues, it is of note that a preclinical study on cardiac dysfunction combining mitochondrial dysfunction

with CoQ10 supplementation substantially improved mitochondrial function and cell survival compared to using either treatment alone [40], and such a combined approach might improve outcome in COQ4 or COQ8A deficient patients.

Preclinical model systems used to study primary CoQ10 deficiency in general terms include yeast (*Saccharomyces cerevisiae*), invertebrates (*Drosophila melanogaster*, *Caenorhabditis elegans*), zebrafish (*Danio rerio*), rodents (principally mutant mice), and human patient derived dermal fibroblasts or induced pluripotent stem cells; however not all of these systems have been utilised for the study of COQ4 or COQ8A deficiencies, particularly with regard to developing therapeutic strategies.

With regard to model systems used to study COQ4 deficiency, at the cellular level these include human induced pluripotent stem cells derived from patient fibroblasts with *COQ4* mutations that replicate low CoQ10 levels and mitochondrial dysfunction. In terms of animal models, *Coq4147c* mice carrying a pathogenic missense mutation in the *CoQ4* gene have been used to study multi-organ CoQ10 deficiency. As noted earlier in this section of the article, the former model system has been used to demonstrate correction of the COQ4 mutation via CRISPR-Cas9 gene editing, with restoration of CoQ10 levels and mitochondrial function [36], with the latter model being used to demonstrate restoration of CoQ10 synthesis following treatment with the CoQ10 lipid nanocarrier BPM31510 [41]. Other than gene editing or use of lipid nanocarriers, model systems have not yet been utilised to investigate the application of any of the other proposed therapeutic strategies outlined above.

As with COQ4 deficiency, preclinical models of COQ8A deficiency include fibroblast based cellular models and mouse models, with the former manifesting low CoQ10 levels and mitochondrial dysfunction, and the latter (*Coq8A* knockout mice) manifesting slowly progressive cerebellar ataxia, Purkinje cell dysfunction, and mild exercise intolerance, closely mimicking human autosomal-recessive cerebellar ataxia type 2 (ARCA2). Collaborative international research initiatives such as the TREAT-ARCA project are working on the development of AAV mediated gene replacement strategies to deliver a functional copy of the human or murine *COQ8A* gene into such pre-clinical mouse models. Otherwise, these model systems have not been used to investigate the application of the therapeutic strategies outlined in the previous sections above.

The situation regarding the proposed therapeutic strategies above is summarised in Table 2. Although there is a precedent for the more general clinical application of many of the therapeutic strategies proposed, for example in the intranasal administration of sumatriptan for the treatment of migraine, or maternal mitochondrial transplantation for children with Pearson's/Kearns-Sayre syndrome, there have been no clinical studies in human subjects (and few preclinical studies) applying such strategies to primary CoQ10 deficiency.

Table 2. Summary of preclinical or clinical studies using proposed treatments for primary CoQ10 deficiency.

Clinical Studies Using Proposed Treatment for Primary CoQ10 Deficiency	Preclinical Studies Using Proposed Treatment for Primary CoQ10 Deficiency	Proposed Treatment
No clinical studies	No preclinical studies	Intranasal administration of CoQ10
No clinical studies	No preclinical studies	Inhibition of LRP1
No clinical studies	No preclinical studies	Activation of SRB1

Table 2. *Cont.*

Clinical Studies Using Proposed Treatment for Primary CoQ10 Deficiency	Preclinical Studies Using Proposed Treatment for Primary CoQ10 Deficiency	Proposed Treatment
No clinical studies	Treatment with CoQ10 lipid nanocarrier BPM31510 restored CoQ9/CoQ10 synthesis in *Coq4147c* mouse model of COQ4 deficiency [41]	Administration of CoQ10 via lipid nanocarriers
No clinical studies	No preclinical studies	Intrastriatal administration of CoQ10
No clinical studies	In vitro study showed 2-propylphenol enhanced activity of isolated COQ8A protein [35]	Stabilisation of complex Q
No clinical studies	CRISPR/Cas9 gene editing technology used to correct *COQ4* mutations in human induced pluripotent stem cells [36]	Gene therapy
No clinical studies	No preclinical studies	Mitochondrial transplantation

6. Conclusions

As noted in the introduction, in this article we have reviewed potential therapeutic strategies relating to two of the primary CoQ10 deficiencies, COQ4 and COQ8A; these disorders have been grouped together because of their complimentary roles in stabilising Complex Q, as well as the difficulty in treating either of these disorders. With regard to COQ8A deficiency, only about 50% of patients have been reported to obtain significant symptomatic benefit following oral CoQ10 supplementation [42]. For patients with COQ4 deficiency resulting from mutations in the *COQ4* gene exons 5–7, individuals typically have a poor response to oral CoQ10 therapy. In the present article we have therefore reviewed alternative therapeutic strategies to conventional oral CoQ10 supplementation for patients with COQ4 or COQ8A deficiency. As both COQ4 and COQ8A deficiencies typically manifest with neurological dysfunction, the access of any proposed therapeutic agent across the human BBB is a major requirement, and methods to potentially address this issue, including the identification of suitable inhibitors or activators of LRP1 or SRB1 transporters respectively, have been reviewed. Other potential therapeutic strategies include the potential stabilisation of Complex Q using agents such as cardiolipin, targetted gene therapy using CRISPR/Cas9 gene-editing or AAV vector gene delivery, or mitochondrial transplantation. It should be emphasised that all of the strategies outlined above, including intranasal administration of CoQ10, inhibition of LRP1, activation of SRB1, administration of CoQ10 via lipid based nanocarriers, stabilisation of Complex Q via cardiolipin/2-propylphenol, use of gene therapy and mitochondrial transplantation are all theoretical proposals with regard to the potential treatment of COQ4 or COQ8A deficiencies in patients, and remain areas for ongoing research.

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