Turton, N, Rutherford, T, Thijssen, DHJ and Hargreaves, IP

Putative adjunct therapies to target mitochondrial dysfunction and oxidative stress in phenylketonuria, lysosomal storage disorders and peroxisomal disorders

Putative adjunct therapies to target mitochondria dysfunction and oxidative stress in Phenylketonuria, Lysosomal storage disorders and Peroxisomal disorders.

Nadia Turton, Tricia Rutherford, Dick Thijssen, Iain P Hargreaves.

Abstract:

Introduction: Oxidative stress (OS) and mitochondrial dysfunction are implicated in the pathogenesis of a number of metabolic diseases. OS occurs when there is an imbalance between the pro-oxidant/antioxidant homeostasis, leading to an increased generation of reactive oxidant species (ROS) with resultant cellular dysfunction. It is becoming apparent that increased ROS generation may be attributable to secondary mitochondrial dysfunction as a consequence of disease pathophysiology. Mitochondrial dysfunction occurs as a result of oxidative damage from enhanced ROS generation as well as the accumulation of toxic metabolites in some metabolic diseases.

Areas covered: The present review will discuss evidence of OS and mitochondrial dysfunction in phenylketonuria (PKU), lysosomal storage disorders (LSDs) and peroxisomal disorders. In addition, potential adjunct therapies which have the potential to enhance mitochondrial functioning and mitigate OS will be explored. The data bases utilised for this review were Pubmed and the Wed of science, with inclusive dates, 1988-2020.

Expert opinion: There is an un-unified approach in the treatment of metabolic diseases. Agents including augmenters of mitochondrial function, antioxidants, and activators of mitochondrial biogenesis, may be beneficial. However, although successful in some cases, these adjunct therapies have yet to be incorporated into the clinical-management of metabolic diseases.

Key words: Metabolic disease, Phenylketonuria, Lysosome storage disorders, Peroxisome disorders, mitochondrial biogenesis, mitochondrial electron transport chain, oxidative stress, antioxidants.

Article highlights

- The metabolic diseases PKU, LSDs and peroxisome disorders have all demonstrated evidence of mitochondrial dysfunction and oxidative stress as part of their disease pathophysiology.
- Certain adjunct therapies have shown to be beneficial in augmenting ETC function and mitigating OS in primary ETC disorders and other diseases associated with similar disease pathophysiology.
- There is still a severe paucity of research of these treatments in IEM, however, they primarily focus on their ability to enhance mitochondrial ETC functioning and mitigating mitochondrial OS.
- Agents which stimulate mitochondrial biogenesis, an integral event which sustains mitochondrial oxidative phosphorylation is gaining more attention in recent years as therapies move from cell-based studies into clinical trials for their ability to improve mitochondrial ETC functioning.
- The therapies discussed are potential adjunct therapies to be taken in conjunction with IEM recommended dietary intervention and primary disease treatments.
- At present, it is difficult to decipher how the treatment of mitochondrial dysfunction and OS in IEM will evolve. A lot of research is still required to evaluate the therapeutic efficacy of

these agents in IEM. However, until biomarkers of mitochondrial dysfunction in IEM patients become more reliable, the therapeutic efficacy of these agents will be difficult to quantify.

1. Introduction

Oxidative stress (OS) and secondary mitochondrial dysfunction have been observed in the pathogenesis of a number of metabolic diseases [1]. OS occurs when there is a disturbed equilibrium between pro-oxidant/antioxidant homeostasis that further leads to the generation of reactive oxygen species (ROS) and other free radicals [2]. The over production of free radicals can cause oxidative damage to biomolecules in the cell including DNA, lipids and proteins, which can be implicated in many chronic diseases [3,4]. The origin of OS can be multifactorial and may be the result of a leakage of electrons from the mitochondrial electron transport chain (ETC) which can occur under physiological conditions, the by-product of enzymatic processes and growth factor activity or occur as a consequence of drugs or toxin exposure [5]. However, emerging evidence suggests that secondary mitochondrial dysfunction could be attributed to the generation of ROS in a number of metabolic diseases [6]. The factors responsible for mitochondrial dysfunction may also be caused by the accumulation of toxic metabolites and by-products in inborn errors of metabolism (IEM) which are also known as metabolic diseases [7]. Alternatively, OS implicated in the pathogenesis of other diseases may lead to direct oxidative damage to the ETC, thus compromising the energy efficiency of the cell [8].

The injurious effects of OS to cellular components and ultimately organ dysfunction observed in multiple IEM validates a need for antioxidant intervention to detoxify ROS, increase the antioxidant capacity of the cell and mitigate mitochondrial dysfunction [9-11]. Recently, a number of novel therapeutic strategies have emerged that target IEM associated OS and may provide potential adjunct treatments for these diseases [12].

The present review aims to discuss the evidence of OS and secondary mitochondrial dysfunction in a range of IEM including, phenylketonuria (PKU), lysosomal storage disorders (LSDs) and peroxisomal disorders, and highlight potential adjunct therapeutic strategies, which target OS and mitochondrial dysfunction which has been associated with these IEM.

2. PKU

PKU is an autosomal recessive metabolic disorder of the amino acid, phenylalanine (Phe). Individuals with PKU have mutations in the gene encoding the hepatic enzyme, phenylalanine hydroxylase (PAH) [13]. This defect in PAH causes an accumulation of Phe in the blood and other tissues with classical PKU patients having blood Phe concentrations exceeding >1200 μmol/L [14]. A proportion of this accumulated Phe will then be metabolized into phenylketones via other metabolic pathways [15].

Neurological impairment is the hallmark of PKU with clinical presentations including microcephaly, developmental delay, psychiatric disorders, cerebral white matter abnormalities and epilepsy [16,17]. However, the new born screening programme has enabled early diagnosis of PKU allowing for a Phe restricted diet to be invoked immediately after diagnosis [18]. Dietary compliance prevents developmental delay and the outcome for individuals who comply diligently is positive. However, there are still reports of changes to MRI scans even in well-controlled dietary groups [19,20]. The low protein diet is an anti-social diet with surveys showing that only 1 in 5 patients comply [19,21-23]. Although a low Phe diet is effective, there remains a paucity of information of how Phe accumulation results in neurological damage. OS and mitochondrial dysfunction have been implicated in the pathophysiology of this disorder and may be significant contributory factors [1].

2.2. Evidence of OS and ETC dysfunction in PKU

OS may be a useful therapeutic target in PKU patients as evidence of OS has been observed on diagnosis and persists, even with dietary compliance [24,25]. In PKU, elevated levels of thiobarbituric-acid reactive species (TBARS ; a product of lipid peroxidation) [24], malondialdehyde (MDA ; product of lipid peroxidation) [26] and 8-hydroxy-2-deoxyguanosine (8-OHdG ; marker of DNA oxidation) have also been reported [27]. This increase in levels of OS identified in PKU may be as a direct result of hyperphenylalaninemia (HPA) induced-ETC impairment, since inhibition of the ETC complexes, particularly complex I (NADH ubiquinone oxidoreductase; EC 1.6.5.3), have been associated with an increase in free radical generation [28,29] (see figure 1). A study by Rech et al [30] identified a reduction in complex I+III (NADH ubiquinone oxidoreductase; EC 1.6.5.3: ubiquinol cytochrome c reductase; EC 1.10.2.2) activity in the brain cortex of chemically induced HPA in rats. However, there was no alteration in the activities of complexes II (succinate ubiquinone reductase; EC 1.3.5.1), II+III (succinate ubiquinone reductase; EC 1.3.5.1: ubiquinol cytochrome c reductase; EC 1.10.2.2) and IV (cytochrome c oxidase; EC 1.9.3.1). It concluded that Phe inhibited the activity of complex I by competing with NADH for active site binding. However, another study identified that hyperphenylalaninemia had no effect on ETC enzyme complex I activity in immortalised human astrocytes [31] and Hargreaves et al [32] identified that elevated Phe concentrations together with dietary restrictions had no effect on complex II+III activity in blood mononuclear cells in a PKU patient population. The paucity of studies identifying the effect of HPA on mitochondrial ETC complexes (in particular complex III activity) as well as evidence of increased lactate levels identified in PKU patients [33], suggests that OS may still occur as a direct result of Phe induced ETC dysfunction, or secondary to an alternative mechanism of Phe induced free radical generation. It should also be noted that in addition to the glial cells including astrocytes, the brain is also composed of neurons. Therefore, it is at present uncertain of the cellular origin of the cerebral ETC dysfunction reported in the study by Rech et al [30]. Although, there was no evidence of astrocytic ETC impairment in the study by Hargreaves et al [31], the effect of Phe exposure on neuronal ETC activity has yet to be examined. Furthermore, we cannot be certain whether Phe-induced mitochondrial dysfunction is cell/tissue specific.

A decrease in cellular antioxidant status has also been reported in PKU patients [27]. A diminution in the level of the naturally occurring brain antioxidant, reduced glutathione (GSH), was found to accompany an increase in OS levels in Wister rat astrocytes treated with Phe (0.5-1.5mM) [34]. A decrease in glutathione peroxidase (Gpx) activity has also been reported in PKU patient erythrocytes [24], which may be associated with reduced cerebral protein synthesis due to the restricted diet or competition between Phe and large neutral amino acids (LNAAs) for the blood brain barrier (BBB) transport [35]. Deficiency in the trace element Selenium (Se) may compromise the efficiency of Gpx, since Se is required for the biological activity of this selenoprotein enzyme [36]. However, a significant decrease in the activity of Gpx has been reported in PKU patients with Se plasma levels within the reference range [37]. Thus, other factors may be responsible for the deficiency in enzyme activity such as Phe induced inhibition [24] (see figure 1). Alternatively, in the brain of hyperphenylalaninemic rats, enhanced degradation as well as a direct suppression of this enzyme have been reported [38].

Interestingly, Phe and its metabolites have been reported to inhibit the activity of 3-hydroxy-3-methylglutaryl-CoA reductase (HMG-CoA reductase), the rate limiting enzyme of the mevalonate pathway [39], and this may be responsible for the reported deficiency in the level of the ETC electron carrier and lipid soluble antioxidant, Coenzyme Q_{10} (CoQ_{10}), in PKU patients [40-44] (see figure 1). The possibility arises that Phe-induced OS may be secondary to a perturbation in cellular antioxidant capacity, identifying the need for therapeutic strategies, which improve cellular antioxidant status and mitigate OS.

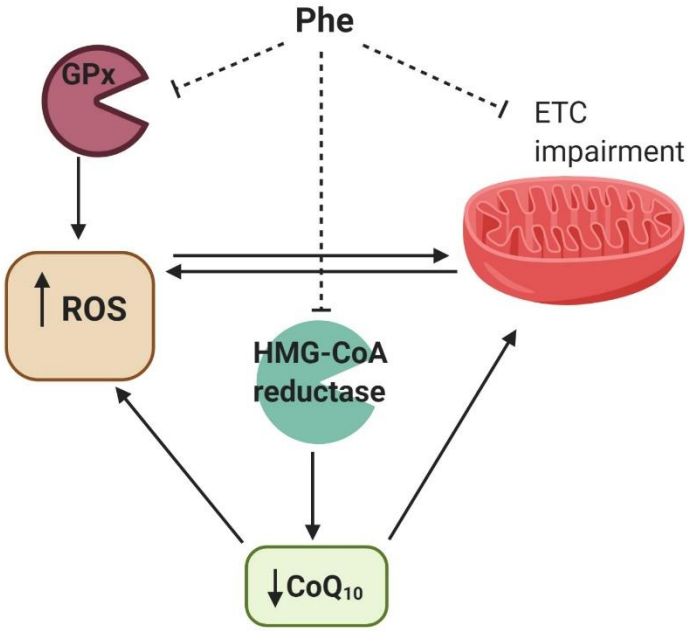

Figure 1. Putative mechanism of oxidative stress and mitochondrial dysfunction in Phenylketonuria (PKU). Abbreviations; Phe: Phenylalanine; ETC: Electron transport chain; CoQ10: Coenzyme Q10; GPx: Glutathione peroxidase; ROS: Reactive oxidant species. Created using BioRender.com.

3. LSDs

The lysosome is a vitally important organelle involved in macromolecule catabolism, recycling and signalling, and defects in these functions, due to defects in the lysosomal acid hydrolase enzymes or cofactors, can result in the accumulation of metabolites which cause cellular toxicity [45]. There are over 70 diseases which are identified as LSDs, most of which are inherited autosomal recessively [45]. Generally, LSDs are categorized according to the type of accumulated macromolecule, with the major categories including glycogenoses, mucopolysaccharidoses and sphingolipidoses [46]. The pathophysiology of LSDs is directly associated with the accumulated toxic metabolite with affected individuals presenting with a wide spectrum of clinical symptoms [47-49]. An accumulation of toxic metabolites may be linked with an increase in lysosomal size/number, which has been associated with an increase in cellular OS, although the mechanisms responsible have yet to be fully elucidated [50]. Alternatively, since lysosomes are essential for autophagy, lysosomal dysfunction in LSDs may result in impaired autophagic clearance of dysfunctional mitochondria [51,52]. The observed accumulation of damaged mitochondria in LSDs has been associated with ROS generation, which may cause further mitochondrial impairment.

3.3. Evidence of OS in LSDs

OS has been associated with the LSD, Gaucher disease (GD) type I [53], which is caused by a deficiency in the lysosomal enzyme, glucocerebrosidase, leading to an accumulation of glucosylceramide and associated multiple organ dysfunction [54,55]. Mello et al [53] identified a significant increase in sulfhydryl (SH) levels in the plasma of GD type I patients compared to healthy controls, which may be associated with the increased lipid peroxidation observed in this disorder. GSH plays a significant role in reducing free radicals, thus becoming oxidised glutathione (GSSG) [56]. Donida et al [57] reported that untreated patients with LSD, Mucopolysaccharidosis type IVA (Moriquo A), had elevated plasma GSH levels as well as increased Gpx activity compared to healthy controls. However, further analysis of the antioxidant defence system in this study identified no alterations in superoxide dismutase (SOD) activity or glutathione reductase (GR) content in Morquio A patients. In this study, the increased Gpx activity may be a consequence of lipid peroxidation which was identified by assessment of urinary 15-F2t-isoprostane levels. Similarly, elevations in MDA levels have also been identified in the blood of Mucopolysaccharidosis (MPS) II patients when compared to controls [58].

Lysosomes contain a high iron content which can in some circumstances generate hydroxyl (OH) radicals via the Fenton reaction [59]. Evidence of increased 8-OHdG excretion in the urine of Morquio A patients compared to healthy controls has been reported, which may be the result of increased OH radical formation [57]. This can oxidise guanosine in mitochondrial and nuclear DNA forming 8-OHdG, thus causing oxidative damage to DNA [57]. The observed increase in ROS may also be due to lysosomal dysfunction in LSD's for example, GD, has been associated with impaired mitophagy resulting in an accumulation of defective mitochondria which can result in an increase in cellular oxidative stress generation (Figure 2) [60]. However, other mechanisms may be responsible for the OS associated with LSDs which have yet to be fully elucidated

3.4. Evidence of ETC dysfunction in LSDs

A decrease in the activities of ETC complexes I, I + III, II, and II + III has been reported in muscle homogenates obtained from patients with lysosomal glycogen storage disorder, Pompe disease [61].

The cause of this global loss of ETC activity reported in the study by Selak et al [61] is as yet uncertain, but may be linked to an increase in ROS generation associated with this LSD. Osellame et al [60] reported that decreased activities of the ETC complexes I and II+III in astrocytes and neurons liberated from a mouse model of GD type II were associated with a reduction in mitochondrial membrane potential, which was maintained by reversal of ATP synthase at the expense of ATP. A decrease in the activities of ETC complexes II, IV and II+III has also been reported in the brain of the murine model of MPS III type C which was also accompanied by a significant decrease in cellular CoQ_{10} status [62]. A deficit in the circulatory level of CoQ_{10} has also been observed in patients with MPS III [63], although evidence of ETC dysfunction has yet to be elucidated. In view of the evidence for the involvement of OS in the pathogenesis of LSDs and the observed depletion in cellular antioxidant status, it may be judicious to consider antioxidant administration as a potential adjunct therapy for LSDs patients.

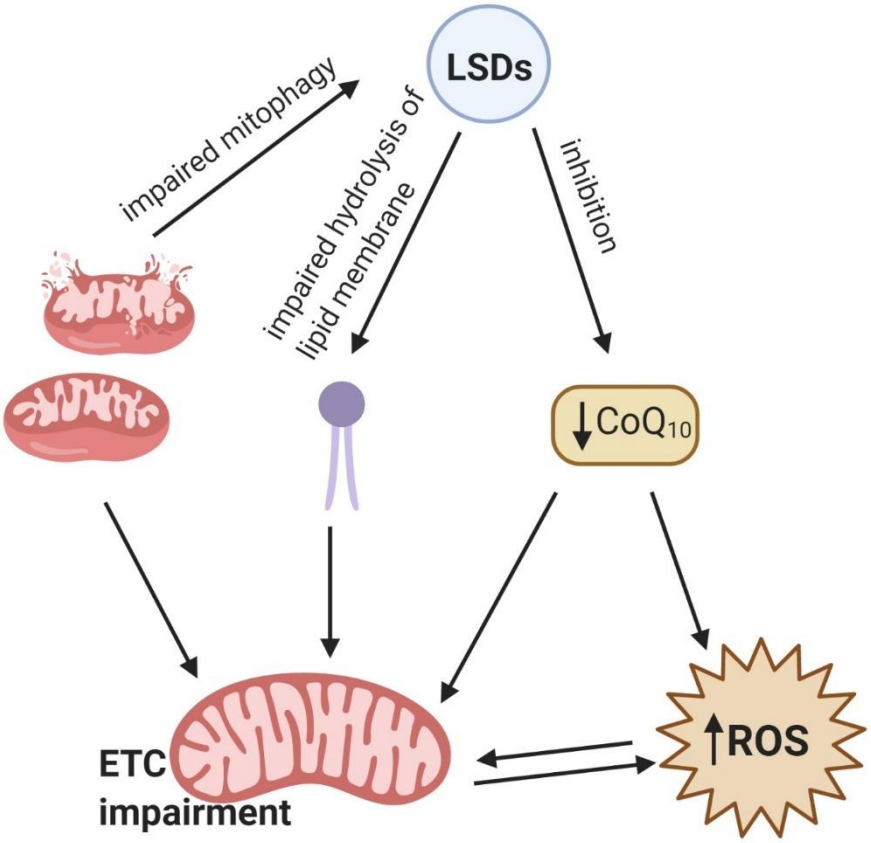

Figure 2. Putative mechanism of oxidative stress and mitochondrial dysfunction in Lysosome storage disorders (LSDs). Abbreviations; CoQ10: Coenzyme Q10; ROS: Reactive oxidant species; ETC: Electron transport chain. Created using BioRender.com.

4. Peroxisomal disorders

Peroxisomes are membrane bound organelles which contain around 50 different enzymes to fulfil their critical roles in a range of metabolic processes including catabolism of polyamines, prostaglandins, purines and eicosanoids, ether phospholipid biosynthesis, fatty acid oxidation, peroxide and ROS metabolism, glyoxylate clearing and possibly the biosynthesis of isoprenoids [64]. Peroxisomal disorders are heterogeneous metabolic diseases that result from either mutations in

genes that encode peroxisomal enzymes (Refsum disease and adrenoleucodystrophy: ALD) [65,66] or occur as the result of defects in peroxisome biogenesis (Zellweger syndrome spectrum disorders and Rhizomelic chondrodysplasia punctate: RCDP) [67]. Peroxisome biogenesis disorders encompass two phenotypic groups: 1. Zellweger syndrome, neonatal ALD and infantile Refsum disease, which all belong to the Zellweger syndrome spectrum of diseases, and 2. RCDP1 [67].

Patients with Zellweger syndrome have defects in the PEX gene encoding peroxins, proteins which are necessary for peroxisome assembly as well as for the import of peroxisomal proteins [68]. The clinical presentations of this disorder include development delay, visual loss from retinal degeneration, liver disease and loss of sensorineural hearing [69]. RCPD patients diagnosed at birth normally do not survive the first decade of life with this disorder characterized by the proximal shortening of the rhizomelia and the femur, punctate calcifications in cartilage, profound growth deficiency, cataracts and neurodevelopmental deficits with defects in plasmalogen biosynthesis [70]. Similarly, the clinical features of ALD present themselves at birth and include muscle hypotonia, severe psychomotor retardation and failure to thrive [71]. Analysis of the post-mortem brains from 4 infants with ALD identified at least two stored lipid products, suggesting at least two enzyme deficiencies in this disorder [71].

4.1. Evidence of OS in peroxisomal disorders

Peroxisomes are considered major sites of ROS generation as a result of their many biosynthetic functions and metabolic activity. For example during beta oxidation of very long-chain fatty acids (VLCFAs), synthesis of bile acids and the production of plasmalogens for the metabolism of myelin lipids, the peroxisome uses oxygen in a number of oxidative reactions which consequently results in the formation of the ROS, H_2O_2 [72]. The peroxisome also contains multiple oxidase enzymes that produce hydrogen peroxide (H_2O_2) as a product of their catalytic activity, for example urate oxidase catalyses the oxidation of uric acid into 5-hydroxyisourate forming H_2O_2 as a by-product [73,74]. Peroxisomes contain a number of antioxidant systems to compensate for the abundance of ROS produced as a result of their metabolic activity [75]. The enzyme, catalase, converts H_2O_2 into oxygen and water and SOD catalyses the dismutation of the superoxide radical into water and oxygen [76,77]. However, in the serum of patients with peroxisome biogenesis disorders, evidence of reduced SOD activity has been reported [78]. These findings accompanied a significant increase in the levels of circulatory MDA and the reactive nitrogen specie (RNS) Nitric oxide (NO). NO may be a product of inducible nitric oxide synthase (INOS) activity which catalyses the oxidation of L-arginine into cirtulline with the concomitant production of NO [79]. NO, although not very reactive itself, is able to form other reactive intermediates which can trigger nitrosative damage to biomolecules [80]. The observed increase in lipid peroxidation, NO production and enhanced levels of H_2O_2 observed in peroxisomal biogenesis disorders, may result from mutations in the PEX gene which is involved in the import of catalase and SOD into the peroxisome [78,81]. Thus, this mutation compromises the peroxisomes ability to detoxify ROS, leaving the cell more susceptible to OS.

Evidence of OS has also been reported in patients who have a defect in the D-bifunctional protein (D-BP) which is involved in the beta-oxidation of VLCFAs [82] (see figure 3). Ferdinandusse et al [82] reported that D-BP patients have elevated circulatory levels of TBAR and 8-OHdG in conjunction with decreased levels of the Lipophilic antioxidants alpha-tocopherol and CoQ_{10}.

4.2. Evidence of ETC dysfunction in peroxisomal disorders

Evidence of ETC impairment has been associated with the accumulation of VLCFAs in patients with X-ALD [83]. This is a peroxisomal disorder caused by mutations in the ABCD1 gene encoding the ABC peroxisome transporter, which is required for the entry of VLCFAs or VLCFA-CoAs into the organelle [84] (see figure 3). Deletion of the ABCD1 gene in B12 oligodendrocytes and U87 astrocytes (cellular model of X-ALD pathology) resulted in a reduction in mitochondrial membrane potential, decreased activity of ETC complex I, as well as ATP synthase with an accompanied reduction in cellular ATP levels [83]. Although the mechanism by which VCFLAs impair mitochondrial function remains to be elucidated, fibroblasts from X-ALD patients with excess VLCFA C26:0 reported evidence of mtDNA oxidation together with impaired ETC activity and enhanced ROS production [85]. This study concluded that excess C26:0 disrupts oxidative phosphorylation and induces ETC ROS generation, in particular at complexes I and II. These free radicals can then oxidize mtDNA, which could contribute to a vicious cycle of mitochondrial dysfunction. Accumulated substances in various peroxisome disorders including VLCFA, phytanic acid and plasmalogens may directly inhibit ETC complex I activity, resulting in upregulated ROS generation [86]. Thus, mitochondrial dysfunction in peroxisome disorders may be a prominent contributor to the increase in OS, implicated in these diseases.

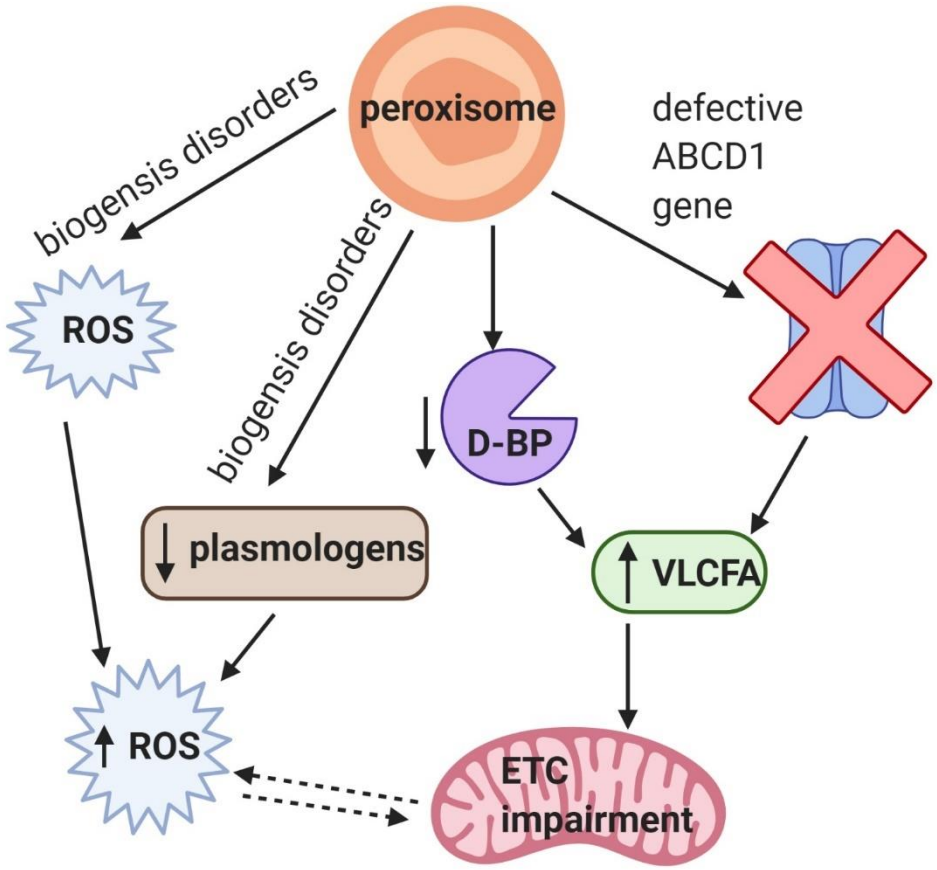

Figure 3. Putative mechanism of oxidative stress and mitochondrial dysfunction in peroxisome disorders. Abbreviations; ROS: Reactive oxidant species; ETC: Electron transport chain; D-BP: D-bifunctional protein; VLCFA: Very long chain fatty acids. Created using BioRender.com.

In PKU, LSDs and peroxisome disorders, the observed imbalance in ROS generation and the ability of the cell to neutralise these species may result from a diminution in antioxidant capacity. If not counteracted, the excess ROS may cause further oxidative damage to cellular organelles including the mitochondria and consequently induce apoptosis (programmed cell death). Therefore, therapeutic strategies that target OS, replenish the cellular antioxidant status and enhance mitochondrial functioning, may prove to be beneficial in patients with these metabolic disorders and therefore will be discussed.

5. Therapeutic strategies that target OS and mitochondria dysfunction

Since ETC dysfunction may be a major contributory factor to the OS reported in PKU, LSDs and peroxisomal disorders, therapeutic strategies that target ETC impairment should be considered and these will be discussed (section 1). Following this, ROS scavenging antioxidants, which directly target OS, will be discussed (section 2). Finally, activators of mitochondrial biogenesis will be considered (section 3). These molecules have been reported to improve cellular energy generation as well as ameliorate OS.

5.1. Section 1: Targets of ETC functioning

5.1.1. CoQ_{10}

The lipid soluble antioxidant, CoQ_{10}, is an essential cofactor of the ETC, where it accepts electrons derived from ETC complexes I and II for transfer to complex III, thus allowing oxidative phosphorylation to occur [87,88] (see figure 4). Interestingly, a deficit in CoQ_{10} concentration has been implicated in the pathophysiology of PKU and LSDs [42,62,82]. The COQ_{10} deficiency observed in these disorders may be attributed to secondary impairment of the CoQ_{10} biosynthetic pathway by metabolites that accumulate in these disorders in addition to ROS induced impairment. In PKU, Phe has been reported to inhibit HMG-CoA reductase activity [39]. In the LSD, MPS III, evidence of a pyridoxal phosphate (PLP) (active form of vitamin B6) deficiency has been reported in addition to a deficit in plasma and cerebrospinal fluid CoQ_{10} status [63]. The accumulated glycosaminoglycan (GAG) in this LSD, heparan sulphate, may bind to PLP which is an essential cofactor for CoQ_{10} biosynthesis [89], resulting in a CoQ_{10} deficiency.

Previous studies have demonstrated that CoQ_{10} treatment is able to improve secondary mitochondrial dysfunction in other diseases where a CoQ_{10} deficiency has been associated with ETC dysfunction. Turton et al [90] demonstrated that CoQ_{10} treatment (5 μM) was able to restore ETC complex II+III activity in organophosphate (OP) treated SH-SY5Y cells. OP treatment has been associated with ROS induced ETC dysfunction and CoQ_{10} deficiency. The ability of exogenous CoQ_{10} to restore complex II+III activity in OP treated cells may be the result of its antioxidant capacity or simply the replenishment of cellular CoQ_{10} status. Duberley et al [91] demonstrated that incubation of CoQ_{10} deficient neurons with exogenous CoQ_{10} (2.5, 5 and 10 μM) induced progressive improvements in ETC enzyme activities. In particular, treatment with 10 μM CoQ_{10} restored ETC complex activity to almost control levels. These studies may support the possibility that ETC dysfunction observed in the IEM may be the result of an underlying CoQ_{10} deficiency. Thus, CoQ_{10} could be administrated as an adjunct therapy to restore endogenous CoQ_{10} status and consequently improve ETC function. Presently, there is no consensus of the dosage of CoQ_{10} that should be administered in the treatment of ETC dysfunction. However, a therapeutic range of 5-50mg/kg/day CoQ_{10} is recommended for primary CoQ_{10} deficiencies in a soluble form for higher bioavailability [87,88]. It should be noted that in previously discussed disease models, a CoQ_{10} concentration of 5 μM and 10 μM was not able to fully restore mitochondrial function [90,91]. This may be due to the low bioavailability of CoQ_{10}, or the fact that approximately only 11% of CoQ_{10}

has been reported to reach the inner mitochondria [92]. Therefore, higher concentrations of CoQ_{10} may be required (>10 μM) to elicit significant improvements in ETC activity.

5.1.2. B vitamins

Dietary vitamin B2 and B3 both play essential roles in the maintenance of mitochondrial functioning. B2 or riboflavin is a precursor of Flavin mononucleotide (FMN) and Flavin adenine dinucleotide (FAD) which are prosthetic groups of ETC complexes I and II, respectively [93]. Vitamin B3 however, encompasses nictonic acid, nicotinamide and nicotinamide riboside (NR), which are precursors of the coenzyme NAD+, and its reduced form NADH [94]. NADH donates two electrons to ETC complex I (see figure 4). A disturbance of B2 metabolism as well as poor absorption has resulted in inadequate cellular levels of FMN and FAD, resulting in mitochondrial dysfunction and riboflavin associated neurodegenerative disorders [93]. When B2 is supplemented or consumed via the diet, it requires specific transporters to convey it from the cytosol into the mitochondria [93]. Interestingly, defects in these riboflavin transporters, for example in brown Vialetto Van Laere disease (disease associated with a Loss-of-function mutations in two riboflavin transporter genes, SLC52A2 and SLC52A3), have been associated with a loss of ETC complex I and II activities in fibroblasts of patients with SLC52A2 mutations [95]. However, Gerards et al [96] reported that in complex I deficient patients (mutations in the ACAD9 gene), complex I activity was increased from 17% to 47% following treatment with 300mg/day riboflavin [96]. It is likely that treatment with riboflavin is able to increase the intra-mitochondrial FAD concentration which compensates for the reduction in the folding capacity of the mutant complex I flavoprotein prosthetic group [97]. Riboflavin has also been demonstrated to promote the assembly of ETC complexes I and IV into the super-complex with complex III, thus enhancing the super-complex formation of the ETC [98]. Therefore, riboflavin treatment may enhance the observed defects in ETC function in IEM in view of its role as a prosthetic group for complexes I and II, as well as its ability to enhance super-complex assembly.

Vitamin B3 is a precursor of NAD(P)+ synthesis, thus the electron carrier NAD(P)H [94]. Treatment with the vitamin B3 analogue, NR, has previously been shown to increase NAD+/NADH levels as well as enhance oxidative phosphorylation [99]. Treatment with NR (101 mg/l) has been reported to protect neuroblastoma cells from MPP+ induced complex I deficiency in a pharmacological model of Parkinson's disease [100]. Since nicotinamide is the precursor of NADH which is required for mitochondrial complex I activity [94], an increase in concentration of this coenzyme may be able to enhance the activity of complex I in IEM. The loss of cerebral complex I activity observed in a mouse model of PKU was suggested to result from Phe competing with NADH to bind to the catalytic site of complex I [30]. Therefore, the use of vitamin B3 in PKU may improve complex I activity by increasing NADH levels, outcompeting Phe, and therefore increasing complex I activity.

Interestingly, vitamin B3 has also been reported to reduce OS [101]. It is proposed that NAD(P)H is able to directly scavenge free radicals and repair the oxidation damage of vital cellular biomolecules. Alternatively, NAD(P)H could function as an indirect operating antioxidant, for example NAD(P)H acts as a hydride donor in the re-reduction of GSSG to GSH, which is catalysed by the enzyme GR [101]. Thus, the increased levels of GSH can reduce free radicals and mitigate OS observed in PKU, LSDs and Peroxisome disorders.

Furthermore, the ability of vitamin B3 to increase ETC activity may be via an upregulation in mitochondrial biogenesis, as NAD+ has been reported to be a rate limiting co-substrate for the sirtuin (SIRT) enzymes [102]. SIRT-1 deacetylates and activates peroxisome proliferator-activator receptor gamma coactivator-1 alpha (PGC1-α), the master regulator of mitochondrial biogenesis [103] (see figure 5). Previous studies have demonstrated that NR supplementation increases NAD+ levels,

activating SIRT-1 and SIRT-3, and consequently enhancing oxidative phosphorylation in rats with high fat diet induced metabolic abnormalities [99]. NR treatment in mitochondrial myopathy mice was also found to induce FOXO1 de-acetylation, which may result from activation of SIRT1 [104]. SIRT1 can activate downstream targets including PGC1-α and mitochondria biogenesis, of which evidence of increased mitochondria biogenesis was detected in this study. Thus, it should be considered that the improvements to mitochondrial functioning post treatment with vitamin B3 may also be the result of increased mitochondria biogenesis [99,100].

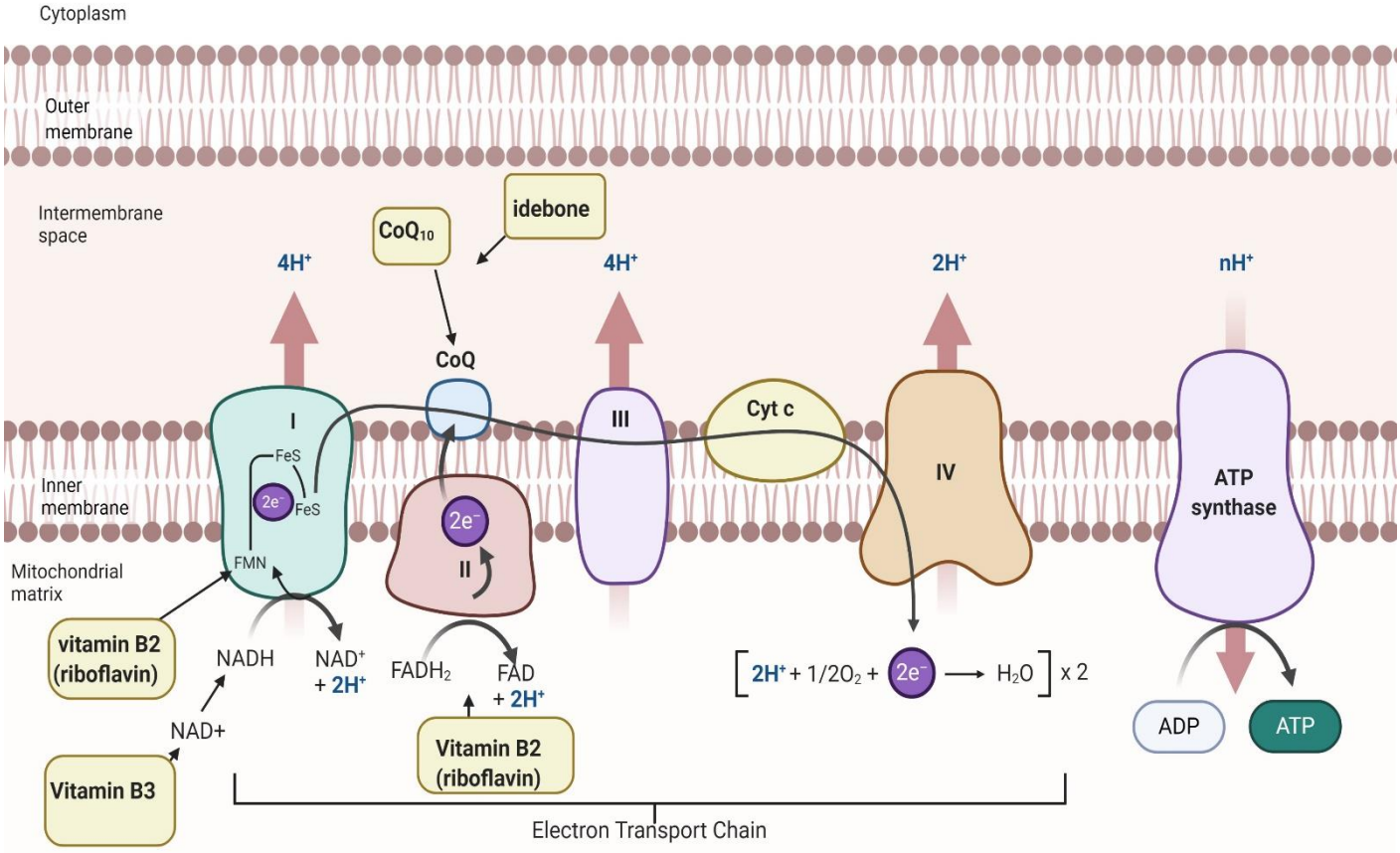

Figure 4. Diagram of electron transport chain (ETC) and ATP synthase illustrating the pumping of H+ ions into the intermembrane space during electron passage, and how the therapeutic strategies discussed can augment mitochondrial functioning. Created using BioRender.com (template provided by Biorender).

5.2. Section 2: Antioxidants

The evidence of increased OS reported in PKU, LSDs and peroxisome disorders recognises a need for enhancement of the cellular antioxidant defence system [58,105]. In these disorders, the origin of OS is generally multifactorial. However, the toxic metabolites which accumulate in these IEM, as well as the ROS and RNS generated during the disease, can directly impair the ETC [30,105]. In the cases of ETC dysfunction, electrons can leak from the chain and partially reduce oxygen, forming the superoxide anion [106]. The increase in ROS generation overwhelms the cellular antioxidant defences resulting in OS. The elevated OS can cause further oxidative damage to the ETC complexes, mtDNA and mitochondrial lipid membrane. These defects can impair mitochondrial function and enhance

further ROS generation, continuing this vicious cycle. Targeting OS by replenishing cellular antioxidant status, by either treatment with molecules that act directly as antioxidants or antioxidant enzyme enhancing therapies, could mitigate the cellular oxidative damage, allowing for improved cellular and organ functioning.

CoQ_{10} previously discussed as an augmenter of mitochondrial ETC functioning, can also be recognised for its antioxidant properties [107]. Antioxidants act by scavenging ROS, protecting cells against OS implicated in the disease pathophysiology [108]. In a cell model of the LSD, GD, CoQ_{10} administration was found to reduce mitochondrial superoxide and H_2O_2 levels [109]. CoQ_{10} administration has also demonstrated antioxidant properties in vivo, following 12 weeks of CoQ_{10} supplementation a significant increase in SOD activity was reported, as well as a decreased levels of MDA (marker of lipid peroxidation) in relapsing-remitting multiple sclerosis patients compared to controls and therefore, may demonstrate similar benefits in IEM patients [107]. However, it has been speculated that CoQ_{10} has poor BBB transport, which could reduce its biochemical efficacy [110]. Thus, other antioxidants could be considered for the treatment of IEM, for example, pyrroloquinoline-quinone (PQQ), vitamin E and lipoic acid have demonstrated abilities to reduce OS in other diseases and therefore should be considered as potential candidates for IEM [111,112]. The clinical application of these antioxidants in relation to combating OS can be found in the following literature [113-118]. Since deficits in GSH status have been reported in IEMs [1,119], therapeutic intervention with EPI-743 may be promising therapeutic agent. Although the mechanism of action of this synthetic quinone is not yet fully elucidated, its ability to transfer electrons from NOQ1 to GR is thought to restore cellular GSH status [120]. For example, administration with EPI-743 significantly increased the level of GSH in lymphocytes from patients with the mitochondrial disease, Leigh syndrome [121]. In addition, N-acetylcysteine, a precursor of GSH [122], which provides cysteine residues (rate limiting substrate for re-synthesis of this tripeptide) [123] enabling the restoration of cellular GSH status, may also be beneficial [124]. Alternatively, idebenone, the short chain analogue of CoQ_{10}, appears to readily cross the BBB and has previously been used to treat mitochondrial dysfunction, for example, idebenone administration has been reported to improve oxidative metabolism in patients with the mitochondrial syndrome, MELAS [125], as well as aide the recovery of visual acuity and prevent loss of colour vision associated which is associated with the mitochondrial disease, Leber hereditary optic neuropathy [126,127]. Thus, idebenone may be considered as an alternative to CoQ_{10} for targeting the observed enhancement of OS in IEM patients, although this therapy may be disease dependent [128].

5.3. Section 3: Activators of mitochondrial biogenesis

Mitochondrial biogenesis is the process by which cells increase in their mitochondrial mass [129]. This integral event sustains oxidative phosphorylation by maintaining a sufficient population of correctly functioning mitochondria, which compensates for the dysfunctional mitochondria.

A number of transcription factors and coactivators are required to execute mitochondrial biogenesis, with the central regulator being transcriptional coactivator PGC-1α, which can further activate numerous transcription factors involved in mitochondrial biogenesis, including nuclear respiratory factors (NRFs) (mitochondrial transcription factor A) which promote expression of Tfam [130].

PGC1-α can be activated by phosphorylation catalysed by activated protein kinase (AMPK), de-acetylation of SIRT1, or by the upregulation of its gene expression by peroxisome proliferation-activated receptor gamma (PPARγ) and cAMP response element binding protein (CREB) [130,131] (see figure 5). Therefore, therapies that activate these factors have the potential to upregulate mitochondrial biogenesis and therefore, the possibility of increasing cellular oxidative

phosphorylation capacity and mitigating OS in IEM. These candidate therapies will be discussed in the following sections.

5.3.1. Pyrroloquinoline quinone

The bioactive compound, PQQ, has been documented for its antioxidant properties, its role in cellular energy metabolism and mitochondrial biogenesis [112,132]. Previous studies have demonstrated its ROS scavenging properties and ability to mitigate mitochondrial-mediated OS [112]. Therefore, PQQ may be an appropriate compound for targeting the increased ROS generation observed in IEM [1]. On a cautionary note, PQQ has been reported to operate in a concentration dependant manner, such that PQQ has exhibited pro-oxidant properties when the concentration of this quinone is above 50 µM [133]. Its reactivity, however, may be dependent on its biological environment.

In addition to its antioxidant properties, PQQ has reported to activate mitochondrial biogenesis [134]. PQQ treatment (4.5 mg/day/kg) of the skeletal muscle from denervated-induced atrophy mice was found to increase the protein expression of the ETC subunits together with the level of PGC-1α [132]. PQQ may activate PGC1-α via CREB, since PQQ may phosphorylate/activate CREB [135]. Activated CREB binds to the PGC1-α promoter, enhancing its transcription [131] (see figure 5). Kuo et al [132] reported that exposure of PQQ (10-30 µM) to mouse Hepa1-6 cells for 24-28 hours resulted in increased citrate synthase (mitochondrial matrix marker) activity together with enhanced ETC complex IV activity. These findings accompanied an increase in PGC-1α mRNA and protein levels as well as increased mRNA expression of NRF-1, NRF-2, Tfam, TFB1M and TFB2M. However, PQQ may activate mitochondrial biogenesis via the NAD+ dependant SIRT-1/PGC-1α pathway (see section 1 for similar mechanism) [136].

5.3.2. Selenium

Se is an essential trace element obtained from normal diet [137]. It has been reported to promote mitochondrial biogenesis by its ability to activate the AKT-CREB pathway and stimulate the PGC-1α signalling cascade [138]. AKT is required to phosphorylate/activate CREB, allowing for CREB binding to the PGC-1α promoter and enhanced transcription [139] (see figure 5). Se treatment has been reported to increase ETC complexes I, II+III and IV activities in murine neuronal HT22 cells [138]. In addition, Se pre-treatment of HT22 cells also reduced hypoxia-induced ROS generation and alleviated hypoxia induced suppression of ETC complex I and IV activities [140]. These findings accompanied an increase in PGC-1α and NRF1 protein levels, suggesting Se induced mitochondrial biogenesis.

Se is also essential for the biological activity of selenoproteins, one of which being the antioxidant enzyme Gpx [141]. Thus, reduced OS associated with Se treatment may be the result of increased activity of this enzyme [140]. Interestingly, alterations to Gpx activity has been observed in PKU and LSDs, which may be attributed to Se deficiency in these disorders [37,57,142]. However, PKU patients with decreased Gpx activity had plasma Se levels within the reference range [37]. In addition, Se supplementation of Se deficient MPS I, II and IV patients demonstrated a decrease in Gpx activity [142]. This may be due to elevated OS prior to Se supplementation, which would require higher levels of enzyme activity.

Se may also be supplemented with CoQ_{10} since these therapies are thought to operate synergistically [143]. Se is a component of the selenoenzyme thioredoxin reductase, which reduces CoQ_{10} to ubiquinol, its antioxidant form [144]. CoQ_{10} also plays a significant role in the synthesis of selenocysteine, a key component of thioredoxin reductase [145]. Thus, a deficiency of Se or CoQ_{10} could affect the recycling process and hinder normal mitochondrial functioning. Se, however, may have a relatively narrow therapeutic window and may be toxic at higher concentrations. Se

supplementation of 300mg/day has been previously recommended for therapeutic potential, however 1000-1600mg/day Se has been intravenously administrated to critically ill patients [143]. At these doses there is no reported evidence of toxicity, however, beyond these therapeutic doses we cannot be certain at present of possible toxic side effects.

5.3.2. Decanoic acid

Decanoic acid (C10), a component of the medium chain triglyceride ketogenic diet, is a ligand for the nuclear receptor PPARγ [146] (see figure 5). This ligand activated transcription factor can upregulate the expression of PGC-1α, thus C10 may have the potential utility in the treatment of ETC dysfunction in IEM [147]. Treatment with C10 in ETC complex I deficient Leigh syndrome (LS) patients increased citrate synthase activity in fibroblasts via the activation of PPARγ [148]. However, not all LS cells responded to C10 treatment, suggesting it could be a patient specific therapy. Treatment with 250 μM C10 over 6 days in SH-SY5Y cells demonstrated an increase in citrate synthase, complex I and catalase activities [149]. Interestingly, various forms of the ketogenic diet (high fat, low carbohydrate diet which promotes the metabolism of fats into ketone bodies, for the body's main energy source) have previously been reported to improve mitochondrial functioning and enhance the antioxidant capacity [150] This is proposed to be via the ability of ketones to activate the Nuclear factor erythroid 2-related factor 2 (NRF2) which upregulates expression of antioxidant proteins, NQO1 and SOD. Interestingly, this study also demonstrates that the ketogenic diet increases succinate levels, allowing substrate flux through ETC complex II and ultimately improving ETC complex II/III activity. As well as this, the ketogenic diet has demonstrated the ability to induce mitochondrial biogenesis [151]. However, on a cautionary note, the ketogenic diet would be impractical for those IEM patients where dietary management is already strict. However, Hughes et al [149] observed that C8 (octanoic acid) and C10 levels are elevated in patients treated with a medium chain triglyceride ketogenic diet. Yet, only C10 (and not C8) has reported to modulate mitochondrial biogenesis, and therefore, this raises the possibility that C10 independently may be an appropriate therapeutic strategy to induce mitochondrial biogenesis. However, further studies will be required to investigate this possibility.

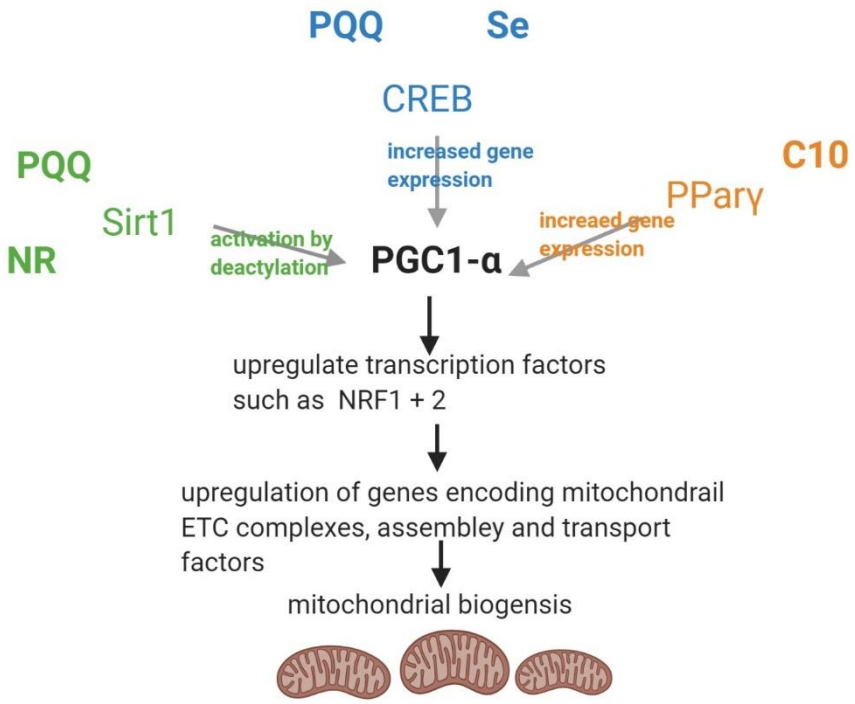

Figure 5. Increase in mitochondrial biogenesis upon activation of PGC1-α By SIRT1, CREB and PParyγ with associated adjunct therapies which stimulate these factors. Abbreviations; PPary: peroxisome proliferator-activated receptor gamma; PGC1-α: peroxisome proliferator-activated receptor gamma coactivator-1 alpha; Sirt1: Sirtuin1; NRF1+2: nuclear respiratory factor 1+2; CREB: cAMP response element binding protein; ETC: Electron transport chain; PQQ: Pyrroloquinoline quinone; Se: Selenium; C10: Decanoic acid; NR: Nicotinamide riboside. Created using BioRender.com.

6. Conclusion

A number of studies have indicated that mitochondrial dysfunction and OS may be important contributory factors to the pathophysiology of PKU, LSDs and peroxisome disorders. The putative adjunct therapies discussed generally focus on enhancement of ETC complex activity and cellular ATP status, ameliorating OS and boosting the cellular antioxidant capacity. Thus, these candidate therapies may be appropriate to target mitochondrial dysfunction and OS in IEM. It should be noted that the strategies discussed are utilised in the treatment of primary ETC disorders and are yet to be considered for the treatment of other disorders. Therefore, studies are still required to evaluate the effects of these therapies in IEM. At present, no consensus exists for the utilisation of these strategies in the treatment of IEM, which may be due to the paucity of data presently available. Moreover, these therapeutic strategies will serve as adjuncts to the currently prescribed therapeutic regimes. Agents that stimulate mitochondrial biogenesis are gaining more attention, in particular for the enhancement of mitochondrial ETC complex activity and therefore may be beneficial in the treatment of IEM.

Although, these therapeutic strategies require further research in cellular IEM models before being translated to human trials.

7. Expert opinion

Although the therapeutic strategies discussed in this review have shown to be beneficial in augmenting ETC function and mitigating OS in primary ETC disorders, there is still a severe paucity of research of these treatments in IEM. In addition, agents that elicit improvement in mitochondrial health via enhancing mitochondrial biogenesis are only recently being translated into human trials. In view of the heterogeneous nature of IEM, candidate therapies may be patient-specific. Therefore, co-supplementation of these therapies should be considered, although the use of combined pharmacotherapies could cause adverse drug interactions, inducing cellular toxicity and severe organ dysfunction. Thus, a single agent, which targets all these aspects in IEM, may be the most suitable option.

Presently, there is still no unified approach to the treatment of specific IEM, with dietary intervention in some cases being the only effective strategy to manage these diseases. However, for IEM patients who are required to comply with dietary management, as in PKU, where dietary management is well recognised as effective, the diet is often abandoned as it is viewed as unpalatable and socially exclusive, with reports of resulting mental health issues [152,153]. It should also be noted that amongst the aging population where IEM screening was not available at birth, dietary intervention was not undertaken, and this group may be susceptible to enhanced oxidative damage and the outcome may be particularly sever, emphasising a need for therapeutic intervention [154].

Evidence for the 'cross-talk' between lysosome and mitochondria is gaining momentum in LSDs since these disorders are known to trigger repression of mitochondrial biogenesis and have impaired autophagic clearance of dysfunctional mitochondria [155,156]. Thus, enhancement of mitochondrial biogenesis to augment ETC complex activity together with enhanced mitophagy to mediate clearance of damaged mitochondria, could be an interesting futuristic approach. The enhancement of TFEB (master regulator of lysosome biogenesis) expression may prove to be beneficial to LSD patients since this has the potential to enhance mitophagy by maintenance of autophagy-lysosome pathway in addition to its ability to induce mitochondrial biogenesis [157]. Thus, regulation of TFEB activity could be a potential therapeutic target for LSD patients. Interestingly, resveratrol (RSV) (10 μM) pre-treatment in human umbilical vein endothelial cells (HUVECs) has shown to upregulate the TFEB and TFEB-modulated downstream gene expression and promoted autophagosome formation. The ability for RSV to upregulate autophagy by inducing TFEB, which promotes formation of autophagosomes and their fusion with the lysosome, also leads to the reduction of OS [158]. In addition, RSV has been shown to induce mitochondrial biogenesis via the SIRT1 pathway [159]. Thus, RSV's multifunctional-role could be a promising prospect for phytochemical intervention in LSDs. However, pharmacological manipulation of phytochemicals may be required to enhance their efficacy. For example, to enhance the selectivity towards the mitochondria they could be conjugated to a mitochondrial-targeting peptide (mitochondria penetrating peptide, mitochondria targeting sequence, SS peptide) of which a similar prospect could be incorporated into the agents presently discussed.

At present, it is difficult to decipher how the treatment of mitochondrial dysfunction and OS in IEM will evolve. A lot of research is still required to evaluate the therapeutic efficacy of these agents in IEM. However, until biomarkers of mitochondrial dysfunction in IEM patients become more reliable, the therapeutic efficacy of these agents will be difficult to quantify.

References

1. Stepien KM, Heaton R, Rankin S, et al. Evidence of Oxidative Stress and Secondary Mitochondrial Dysfunction in Metabolic and Non-Metabolic Disorders. J Clin Med. 2017;6(7):71.
2. Uttara B, Singh AV, Zamboni P, et al. Oxidative stress and neurodegenerative diseases: a review of upstream and downstream antioxidant therapeutic options. Current neuropharmacology. 2009;7(1):65-74.
3. Therond P. [Oxidative stress and damages to biomolecules (lipids, proteins, DNA)]. Ann Pharm Fr. 2006 Nov;64(6):383-9.
4. Sunday O, Adekunle M, Temitope O, et al. Alteration in antioxidants level and lipid peroxidation of patients with neurodegenerative diseases {Alzheimer's disease and Parkinson disease} [Original Article]. International Journal of Nutrition, Pharmacology, Neurological Diseases. 2014 July 1, 2014;4(3):146-152.
5. Burton GJ, Jauniaux E. Oxidative stress. Best practice & research Clinical obstetrics & gynaecology. 2011;25(3):287-299.
6. Pelicano H, Lu W, Zhou Y, et al. Mitochondrial Dysfunction and Reactive Oxygen Species Imbalance Promote Breast Cancer Cell Motility through a CXCL14-Mediated Mechanism. Cancer Research. 2009;69(6):2375-2383.
7. Kolker S, Schwab M, Horster F, et al. Methylmalonic acid, a biochemical hallmark of methylmalonic acidurias but no inhibitor of mitochondrial respiratory chain. J Biol Chem. 2003 Nov 28;278(48):47388-93.
8. Brealey D, Brand M, Hargreaves I, et al. Association between mitochondrial dysfunction and severity and outcome of septic shock. The Lancet. 2002;360(9328):219-223.
9. Ogura S, Shimosawa T. Oxidative stress and organ damages. Curr Hypertens Rep. 2014 Aug;16(8):452.
10. Lorente L. New Prognostic Biomarkers of Mitochondrial Oxidative Stress in Septic Patients [Review Article]. Arch Crit Care Med. 2015;1(2):e3125.
11. Reddy PH, Manczak M, Yin X, et al. Protective Effects of Indian Spice Curcumin Against Amyloid-β in Alzheimer's Disease. Journal of Alzheimer's disease : JAD. 2018;61(3):843-866.
12. Martinez-Cruz F, Pozo D, Osuna C, et al. Oxidative stress induced by phenylketonuria in the rat: Prevention by melatonin, vitamin E, and vitamin C. Journal of Neuroscience Research. 2002;69(4):550-558.
13. Zhou Y-A, Ma Y-X, Zhang Q-B, et al. Mutations of the phenylalanine hydroxylase gene in patients with phenylketonuria in Shanxi, China. Genetics and molecular biology. 2012;35(4):709-713.
14. Vockley J, Andersson HC, Antshel KM, et al. Phenylalanine hydroxylase deficiency: diagnosis and management guideline. Genetics in Medicine. 2014 2014/02/01;16(2):188-200.
15. Krause W, Halminski M, McDonald L, et al. Biochemical and neuropsychological effects of elevated plasma phenylalanine in patients with treated phenylketonuria. A model for the study of phenylalanine and brain function in man. J Clin Invest. 1985 Jan;75(1):40-8.
16. Pietz J. Neurological aspects of adult phenylketonuria. Current Opinion in Neurology. 1998;11(6):679-688.
17. Targum SD, Lang W. Neurobehavioral problems associated with phenylketonuria. Psychiatry (Edgmont (Pa : Township)). 2010;7(12):29-32.
18. Vist GE, Fronsdal KB, Johansen M, et al. NIPH Systematic Reviews: Executive Summaries. Newborn Screening for Inborn Errors of Metabolism. Oslo, Norway: Knowledge Centre for the Health Services at The Norwegian Institute of Public Health (NIPH)

19. Das AM, Goedecke K, Meyer U, et al. Dietary habits and metabolic control in adolescents and young adults with phenylketonuria: self-imposed protein restriction may be harmful. JIMD reports. 2014;13:149-158.
20. Ding X-Q, Fiehler J, Kohlschütter B, et al. MRI abnormalities in normal-appearing brain tissue of treated adult PKU patients. Journal of Magnetic Resonance Imaging. 2008;27(5):998-1004.
21. Vieira EN, Maia HSF, Monteiro CB, et al. Quality of life and adherence to treatment in early-treated Brazilian phenylketonuria pediatric patients. Brazilian journal of medical and biological research = Revista brasileira de pesquisas medicas e biologicas. 2017;51(2):e6709-e6709.
22. Weglage J, Pietsch M, Funders B, et al. Neurological findings in early treated phenylketonuria. Acta Paediatr. 1995 Apr;84(4):411-5.
23. Cazzorla C, Bensi G, Biasucci G, et al. Living with phenylketonuria in adulthood: The PKU ATTITUDE study. Molecular genetics and metabolism reports. 2018;16:39-45.
24. Sirtori LR, Dutra-Filho CS, Fitarelli D, et al. Oxidative stress in patients with phenylketonuria. Biochim Biophys Acta. 2005 Apr 15;1740(1):68-73.
25. Sitta A, Barschak AG, Deon M, et al. Investigation of oxidative stress parameters in treated phenylketonuric patients. Metab Brain Dis. 2006 Dec;21(4):287-96.
26. Ercal N, Aykin-Burns N, Gurer-Orhan H, et al. Oxidative stress in a phenylketonuria animal model. Free Radic Biol Med. 2002 May 1;32(9):906-11.
27. Schulpis KH, Tsakiris S, Traeger-Synodinos J, et al. Low total antioxidant status is implicated with high 8-hydroxy-2-deoxyguanosine serum concentrations in phenylketonuria. Clin Biochem. 2005 Mar;38(3):239-42.
28. Ide T, Tsutsui H, Kinugawa S, et al. Mitochondrial Electron Transport Complex I Is a Potential Source of Oxygen Free Radicals in the Failing Myocardium. Circulation Research. 1999;85(4):357-363.
29. Matsuzaki S, Szweda PA, Szweda LI, et al. Regulated production of free radicals by the mitochondrial electron transport chain: Cardiac ischemic preconditioning. Advanced drug delivery reviews. 2009;61(14):1324-1331.
30. Rech VC, Feksa LR, Dutra-Filho CS, et al. Inhibition of the mitochondrial respiratory chain by phenylalanine in rat cerebral cortex. Neurochem Res. 2002 May;27(5):353-7.
31. Kyprianou N, Murphy E, Lee P, et al. Assessment of mitochondrial respiratory chain function in hyperphenylalaninaemia. Journal of Inherited Metabolic Disease. 2009 2009/04/01;32(2):289-296.
32. Hargreaves IP, Heales SJ, Briddon A, et al. Blood mononuclear cell coenzyme Q10 concentration and mitochondrial respiratory chain succinate cytochrome-c reductase activity in phenylketonuric patients. J Inherit Metab Dis. 2002 Dec;25(8):673-9.
33. Halestrap AP, Brand MD, Denton RM. Inhibition of mitochondrial pyruvate transport by phenylpyruvate and α-ketoisocaproate. Biochimica et Biophysica Acta (BBA) - Biomembranes. 1974 1974/10/10/;367(1):102-108.
34. Preissler T, Bristot IJ, Costa BM, et al. Phenylalanine induces oxidative stress and decreases the viability of rat astrocytes: possible relevance for the pathophysiology of neurodegeneration in phenylketonuria. Metab Brain Dis. 2016 Jun;31(3):529-37.
35. de Groot MJ, Sijens PE, Reijngoud D-J, et al. Phenylketonuria: brain phenylalanine concentrations relate inversely to cerebral protein synthesis. Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism. 2015;35(2):200-205.
36. Hatanaka N, Nakaden H, Yamamoto Y, et al. Selenium kinetics and changes in glutathione peroxidase activities in patients receiving long-term parenteral nutrition and effects of supplementation with selenite. Nutrition. 2000 Jan;16(1):22-6.

37. Sanayama Y, Nagasaka H, Takayanagi M, et al. Experimental evidence that phenylalanine is strongly associated to oxidative stress in adolescents and adults with phenylketonuria. Mol Genet Metab. 2011 Jul;103(3):220-5.
38. Kienzle Hagen ME, Pederzolli CD, Sgaravatti AM, et al. Experimental hyperphenylalaninemia provokes oxidative stress in rat brain. Biochim Biophys Acta. 2002 Apr 24;1586(3):344-52.
39. Castillo M, Zafra MF, Garcia-Peregrin E. Inhibition of brain and liver 3-hydroxy-3-methylglutaryl-CoA reductase and mevalonate-5-pyrophosphate decarboxylase in experimental hyperphenylalaninemia. Neurochemical Research. 1988 1988/06/01;13(6):551-555.
40. Shefer S, Tint GS, Jean-Guillaume D, et al. Is there a relationship between 3-hydroxy-3-methylglutaryl coenzyme a reductase activity and forebrain pathology in the PKU mouse? J Neurosci Res. 2000 Sep 1;61(5):549-63.
41. Montero R, Yubero D, Salgado MC, et al. Plasma coenzyme Q(10) status is impaired in selected genetic conditions. Scientific reports. 2019;9(1):793-793.
42. Artuch R, Colomé C, Vilaseca MA, et al. Plasma phenylalanine is asociated with decreased serum ubiquine-10 concentrations in phenylketonuria. Journal of Inherited Metabolic Disease. 2001 2001/06/01;24(3):359-366.
43. Zhong X, Yi X, da Silveira E Sá RdC, et al. CoQ10 Deficiency May Indicate Mitochondrial Dysfunction in Cr(VI) Toxicity. Int J Mol Sci. 2017;18(4):816.
44. Miyamae T, Seki M, Naga T, et al. Increased oxidative stress and coenzyme Q10 deficiency in juvenile fibromyalgia: amelioration of hypercholesterolemia and fatigue by ubiquinol-10 supplementation. Redox Report. 2013 2013/01/01;18(1):12-19.
45. Platt FM, d'Azzo A, Davidson BL, et al. Lysosomal storage diseases. Nature Reviews Disease Primers. 2018 2018/10/01;4(1):27.
46. Sun A. Lysosomal storage disease overview. Ann Transl Med. 2018;6(24):476-476.
47. Ferreira CR, Gahl WA. Lysosomal storage diseases. Translational science of rare diseases. 2017;2(1-2):1-71.
48. Folts CJ, Scott-Hewitt N, Pröschel C, et al. Lysosomal Re-acidification Prevents Lysosphingolipid-Induced Lysosomal Impairment and Cellular Toxicity. PLOS Biology. 2016;14(12):e1002583.
49. Wraith JE. The clinical presentation of lysosomal storage disorders. Acta Neurol Taiwan. 2004 Sep;13(3):101-6.
50. Donida B, Jacques CED, Mescka CP, et al. Oxidative damage and redox in Lysosomal Storage Disorders: Biochemical markers. Clinica Chimica Acta. 2017 2017/03/01/;466:46-53.
51. Demine S, Michel S, Vannuvel K, et al. Macroautophagy and cell responses related to mitochondrial dysfunction, lipid metabolism and unconventional secretion of proteins. Cells. 2012 Jun 20;1(2):168-203.
52. Platt FM, Boland B, van der Spoel AC. The cell biology of disease: lysosomal storage disorders: the cellular impact of lysosomal dysfunction. J Cell Biol. 2012 Nov 26;199(5):723-34.
53. Mello AS, da Silva Garcia C, de Souza Machado F, et al. Oxidative stress parameters of Gaucher disease type I patients. Molecular genetics and metabolism reports. 2015;4:1-5.
54. Beutler E, Demina A, Gelbart T. Glucocerebrosidase mutations in Gaucher disease. Molecular medicine (Cambridge, Mass). 1994;1(1):82-92.
55. Stirnemann J, Belmatoug N, Camou F, et al. A Review of Gaucher Disease Pathophysiology, Clinical Presentation and Treatments. Int J Mol Sci. 2017;18(2):441.
56. Forman HJ, Zhang H, Rinna A. Glutathione: overview of its protective roles, measurement, and biosynthesis. Molecular aspects of medicine. 2009 Feb-Apr;30(1-2):1-12.
57. Donida B, Marchetti DP, Jacques CED, et al. Oxidative profile exhibited by Mucopolysaccharidosis type IVA patients at diagnosis: Increased keratan urinary levels. Molecular genetics and metabolism reports. 2017;11:46-53.

58. Filippon L, Vanzin CS, Biancini GB, et al. Oxidative stress in patients with mucopolysaccharidosis type II before and during enzyme replacement therapy. Molecular Genetics and Metabolism. 2011 2011/06/01/;103(2):121-127.
59. Kwan WP, Voelker BM. Rates of Hydroxyl Radical Generation and Organic Compound Oxidation in Mineral-Catalyzed Fenton-like Systems. Environmental Science & Technology. 2003 2003/03/01;37(6):1150-1158.
60. Osellame LD, Rahim AA, Hargreaves IP, et al. Mitochondria and quality control defects in a mouse model of Gaucher disease--links to Parkinson's disease. Cell Metab. 2013;17(6):941-953.
61. Selak MA, de Chadarevian JP, Melvin JJ, et al. Mitochondrial activity in Pompe's disease. Pediatr Neurol. 2000 Jul;23(1):54-7.
62. Martins C, Hůlková H, Dridi L, et al. Neuroinflammation, mitochondrial defects and neurodegeneration in mucopolysaccharidosis III type C mouse model. Brain : a journal of neurology. 2015;138(Pt 2):336-355.
63. Yubero D, Montero R, O'Callaghan M, et al. Coenzyme Q(10) and Pyridoxal Phosphate Deficiency Is a Common Feature in Mucopolysaccharidosis Type III. JIMD reports. 2016;25:1-7.
64. Delille HK, Bonekamp NA, Schrader M. Peroxisomes and disease - an overview. International journal of biomedical science : IJBS. 2006;2(4):308-314.
65. Wierzbicki AS, Lloyd MD, Schofield CJ, et al. Refsum's disease: a peroxisomal disorder affecting phytanic acid alpha-oxidation. J Neurochem. 2002 Mar;80(5):727-35.
66. Leipnitz G, Amaral AU, Fernandes CG, et al. Pristanic acid promotes oxidative stress in brain cortex of young rats: a possible pathophysiological mechanism for brain damage in peroxisomal disorders. Brain Res. 2011 Mar 25;1382:259-65.
67. Argyriou C, D'Agostino MD, Braverman N. Peroxisome biogenesis disorders. Translational science of rare diseases. 2016;1(2):111-144.
68. Suzuki Y, Shimozawa N, Orii T, et al. Genetic and molecular bases of peroxisome biogenesis disorders. Genetics in Medicine. 2001 2001/09/01;3(5):372-376.
69. Baumgartner MR, Poll-The BT, Verhoeven NM, et al. Clinical approach to inherited peroxisomal disorders: a series of 27 patients. Ann Neurol. 1998 Nov;44(5):720-30.
70. Bams-Mengerink AM, Koelman JHTM, Waterham H, et al. The neurology of rhizomelic chondrodysplasia punctata. Orphanet Journal of Rare Diseases. 2013 2013/10/30;8(1):174.
71. Farrell DF. Neonatal adrenoleukodystrophy: a clinical, pathologic, and biochemical study. Pediatr Neurol. 2012 Nov;47(5):330-6.
72. Krysko O, Bottelbergs A, Van Veldhoven P, et al. Combined deficiency of peroxisomal beta-oxidation and ether lipid synthesis in mice causes only minor cortical neuronal migration defects but severe hypotonia. Mol Genet Metab. 2010 May;100(1):71-6.
73. Fransen M, Nordgren M, Wang B, et al. Role of peroxisomes in ROS/RNS-metabolism: implications for human disease. Biochim Biophys Acta. 2012 Sep;1822(9):1363-73.
74. Gabison L, Prangé T, Colloc'h N, et al. Structural analysis of urate oxidase in complex with its natural substrate inhibited by cyanide: mechanistic implications. BMC structural biology. 2008;8:32-32.
75. Pascual-Ahuir A, Manzanares-Estreder S, Proft M. Pro- and Antioxidant Functions of the Peroxisome-Mitochondria Connection and Its Impact on Aging and Disease. Oxidative medicine and cellular longevity. 2017;2017:9860841-9860841.
76. Heck DE, Shakarjian M, Kim HD, et al. Mechanisms of oxidant generation by catalase. Annals of the New York Academy of Sciences. 2010;1203:120-125.
77. Fridovich I. Superoxide radical and superoxide dismutases. Annu Rev Biochem. 1995;64:97-112.
78. El-Bassyouni HT, Abdel Maksoud SA, Salem FA, et al. Evidence of oxidative stress in peroxisomal disorders. Singapore Med J. 2012 Sep;53(9):608-14.

79. Förstermann U, Sessa WC. Nitric oxide synthases: regulation and function. European heart journal. 2012;33(7):829-837d.
80. Phaniendra A, Jestadi DB, Periyasamy L. Free radicals: properties, sources, targets, and their implication in various diseases. Indian journal of clinical biochemistry : IJCB. 2015;30(1):11-26.
81. Waterham HR, Ebberink MS. Genetics and molecular basis of human peroxisome biogenesis disorders. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease. 2012 2012/09/01/;1822(9):1430-1441.
82. Ferdinandusse S, Finckh B, de Hingh YC, et al. Evidence for increased oxidative stress in peroxisomal D-bifunctional protein deficiency. Mol Genet Metab. 2003 Aug;79(4):281-7.
83. Baarine M, Beeson C, Singh A, et al. ABCD1 deletion-induced mitochondrial dysfunction is corrected by SAHA: implication for adrenoleukodystrophy. J Neurochem. 2015 May;133(3):380-96.
84. Kemp S, Theodoulou FL, Wanders RJA. Mammalian peroxisomal ABC transporters: from endogenous substrates to pathology and clinical significance. British journal of pharmacology. 2011;164(7):1753-1766.
85. Lopez-Erauskin J, Galino J, Ruiz M, et al. Impaired mitochondrial oxidative phosphorylation in the peroxisomal disease X-linked adrenoleukodystrophy. Hum Mol Genet. 2013 Aug 15;22(16):3296-305.
86. Schönfeld P, Reiser G. Rotenone-like Action of the Branched-chain Phytanic Acid Induces Oxidative Stress in Mitochondria. Journal of Biological Chemistry. 2006 March 17, 2006;281(11):7136-7142.
87. Neergheen V, Chalasani A, Wainwright L, et al. Coenzyme Q10 in the Treatment of Mitochondrial Disease. Journal of Inborn Errors of Metabolism and Screening. 2017;5.
88. Hargreaves IP. Coenzyme Q10 as a therapy for mitochondrial disease. Int J Biochem Cell Biol. 2014 Apr;49:105-11.
89. Huang Y, Liu X, Cui Z, et al. Pyridoxal-5'-phosphate as an oxygenase cofactor: Discovery of a carboxamide-forming, α-amino acid monooxygenase-decarboxylase. Proceedings of the National Academy of Sciences. 2018;115(5):974-979.
90. Turton N, Heaton RA, Ismail F, et al. The Effect of Organophosphate Exposure on Neuronal Cell Coenzyme Q10 Status. Neurochem Res. 2020 Apr 18.
91. Duberley KE, Heales SJR, Abramov AY, et al. Effect of Coenzyme Q10 supplementation on mitochondrial electron transport chain activity and mitochondrial oxidative stress in Coenzyme Q10 deficient human neuronal cells. The International Journal of Biochemistry & Cell Biology. 2014 2014/05/01/;50:60-63.
92. Bentinger M, Brismar K, Dallner G. The antioxidant role of coenzyme Q. Mitochondrion. 2007 Jun;7 Suppl:S41-50.
93. Udhayabanu T, Manole A, Rajeshwari M, et al. Riboflavin Responsive Mitochondrial Dysfunction in Neurodegenerative Diseases. J Clin Med. 2017 May 5;6(5).
94. Sauve AA. NAD⁺ and Vitamin B₃: From Metabolism to Therapies. Journal of Pharmacology and Experimental Therapeutics. 2008;324(3):883-893.
95. Manole A, Jaunmuktane Z, Hargreaves I, et al. Clinical, pathological and functional characterization of riboflavin-responsive neuropathy. Brain : a journal of neurology. 2017;140(11):2820-2837.
96. Gerards M, van den Bosch BJC, Danhauser K, et al. Riboflavin-responsive oxidative phosphorylation complex I deficiency caused by defective ACAD9: new function for an old gene. Brain. 2010;134(1):210-219.
97. Olsen RK, Olpin SE, Andresen BS, et al. ETFDH mutations as a major cause of riboflavin-responsive multiple acyl-CoA dehydrogenation deficiency. Brain. 2007 Aug;130(Pt 8):2045-54.
98. Grad LI, Lemire BD. Riboflavin enhances the assembly of mitochondrial cytochrome c oxidase in C. elegans NADH-ubiquinone oxidoreductase mutants. Biochim Biophys Acta. 2006 Feb;1757(2):115-22.

99. Cantó C, Houtkooper Riekelt H, Pirinen E, et al. The NAD+ Precursor Nicotinamide Riboside Enhances Oxidative Metabolism and Protects against High-Fat Diet-Induced Obesity. Cell Metab. 2012 2012/06/06/;15(6):838-847.
100. Jia H, Li X, Gao H, et al. High doses of nicotinamide prevent oxidative mitochondrial dysfunction in a cellular model and improve motor deficit in a Drosophila model of Parkinson's disease. Journal of Neuroscience Research. 2008;86(9):2083-2090.
101. KIRSCH M, GROOT HD. NAD(P)H, a directly operating antioxidant? The FASEB Journal. 2001;15(9):1569-1574.
102. Cantó C, Menzies KJ, Auwerx J. NAD(+) Metabolism and the Control of Energy Homeostasis: A Balancing Act between Mitochondria and the Nucleus. Cell Metab. 2015;22(1):31-53.
103. Rodgers JT, Lerin C, Gerhart-Hines Z, et al. Metabolic adaptations through the PGC-1 alpha and SIRT1 pathways. FEBS letters. 2008;582(1):46-53.
104. Khan NA, Auranen M, Paetau I, et al. Effective treatment of mitochondrial myopathy by nicotinamide riboside, a vitamin B3. EMBO molecular medicine. 2014;6(6):721-731.
105. Heaton R, Millichap L, Saleem F, et al. Current biochemical treatments of mitochondrial respiratory chain disorders. Expert Opinion on Orphan Drugs. 2019 2019/06/03;7(6):277-285.
106. Turrens JF. Mitochondrial formation of reactive oxygen species. The Journal of physiology. 2003;552(Pt 2):335-344.
107. Sanoobar M, Eghtesadi S, Azimi A, et al. Coenzyme Q10 supplementation reduces oxidative stress and increases antioxidant enzyme activity in patients with relapsing-remitting multiple sclerosis. Int J Neurosci. 2013 Nov;123(11):776-82.
108. Poljsak B, Šuput D, Milisav I. Achieving the Balance between ROS and Antioxidants: When to Use the Synthetic Antioxidants. Oxidative Medicine and Cellular Longevity. 2013 2013/04/29;2013:956792.
109. de la Mata M, Cotán D, Oropesa-Ávila M, et al. Coenzyme Q(10) partially restores pathological alterations in a macrophage model of Gaucher disease. Orphanet journal of rare diseases. 2017;12(1):23-23.
110. Wainwright L. Mechanisms of Coenzyme Q10 Blood-Brain Barrier Transport 2018.
111. Baumgartner S, Mensink RP, Haenen GR, et al. The effects of vitamin E or lipoic acid supplementation on oxyphytosterols in subjects with elevated oxidative stress: a randomized trial. Scientific Reports. 2017 2017/11/10;7(1):15288.
112. Maharjan S, Sakai Y, Hoseki J. Screening of dietary antioxidants against mitochondria-mediated oxidative stress by visualization of intracellular redox state. Bioscience, Biotechnology, and Biochemistry. 2016 2016/04/02;80(4):726-734.
113. Harris CB, Chowanadisai W, Mishchuk DO, et al. Dietary pyrroloquinoline quinone (PQQ) alters indicators of inflammation and mitochondrial-related metabolism in human subjects. J Nutr Biochem. 2013 Dec;24(12):2076-84.
114. Derosa G, D'Angelo A, Romano D, et al. A Clinical Trial about a Food Supplement Containing α-Lipoic Acid on Oxidative Stress Markers in Type 2 Diabetic Patients. Int J Mol Sci. 2016;17(11):1802.
115. Khalili M, Eghtesadi S, Mirshafiey A, et al. Effect of lipoic acid consumption on oxidative stress among multiple sclerosis patients: a randomized controlled clinical trial. Nutr Neurosci. 2014 Jan;17(1):16-20.
116. McMackin CJ, Widlansky ME, Hamburg NM, et al. Effect of combined treatment with alpha-Lipoic acid and acetyl-L-carnitine on vascular function and blood pressure in patients with coronary artery disease. J Clin Hypertens (Greenwich). 2007 Apr;9(4):249-55.
117. Zhang L, Zhang Z, Khan A, et al. Advances in drug therapy for mitochondrial diseases. Ann Transl Med. 2020;8(1):17-17.
118. Polyak E, Ostrovsky J, Peng M, et al. N-acetylcysteine and vitamin E rescue animal longevity and cellular oxidative stress in pre-clinical models of mitochondrial complex I disease. Molecular Genetics and Metabolism. 2018 2018/04/01/;123(4):449-462.

119. Fernandes CG, Leipnitz G, Seminotti B, et al. Experimental evidence that phenylalanine provokes oxidative stress in hippocampus and cerebral cortex of developing rats. Cell Mol Neurobiol. 2010 Mar;30(2):317-26.
120. Martinelli D, Catteruccia M, Piemonte F, et al. EPI-743 reverses the progression of the pediatric mitochondrial disease--genetically defined Leigh Syndrome. Mol Genet Metab. 2012 Nov;107(3):383-8.
121. Enns GM, Cowan TM. Glutathione as a Redox Biomarker in Mitochondrial Disease-Implications for Therapy. J Clin Med. 2017 [cited. DOI:10.3390/jcm6050050 http://europepmc.org/abstract/MED/28467362

https://doi.org/10.3390/jcm6050050

https://europepmc.org/articles/PMC5447941
122. Tardiolo G, Bramanti P, Mazzon E. Overview on the Effects of N-Acetylcysteine in Neurodegenerative Diseases. Molecules (Basel, Switzerland). 2018;23(12):3305.
123. Reyes RC, Cittolin-Santos GF, Kim J-E, et al. Neuronal Glutathione Content and Antioxidant Capacity can be Normalized In Situ by N-acetyl Cysteine Concentrations Attained in Human Cerebrospinal Fluid. Neurotherapeutics : the journal of the American Society for Experimental NeuroTherapeutics. 2016;13(1):217-225.
124. Kerksick C, Willoughby D. The Antioxidant Role of Glutathione and N-Acetyl-Cysteine Supplements and Exercise-Induced Oxidative Stress. Journal of the International Society of Sports Nutrition. 2005 2005/12/01;2(2):38.
125. Ikejiri Y, Mori E, Ishii K, et al. Idebenone improves cerebral mitochondrial oxidative metabolism in a patient with MELAS. Neurology. 1996 Aug;47(2):583-5.
126. Klopstock T, Yu-Wai-Man P, Dimitriadis K, et al. A randomized placebo-controlled trial of idebenone in Leber's hereditary optic neuropathy. Brain. 2011 Sep;134(Pt 9):2677-86.
127. Rudolph G, Dimitriadis K, Büchner B, et al. Effects of idebenone on color vision in patients with leber hereditary optic neuropathy. J Neuroophthalmol. 2013 2013/03//;33(1):30-36.
128. Kerr DS. Review of clinical trials for mitochondrial disorders: 1997-2012. Neurotherapeutics. 2013 Apr;10(2):307-19.
129. Chan SHH, Chan JYH. Mitochondria and Reactive Oxygen Species Contribute to Neurogenic Hypertension. Physiology. 2017;32(4):308-321.
130. Jornayvaz FR, Shulman GI. Regulation of mitochondrial biogenesis. Essays in biochemistry. 2010;47:69-84.
131. Fernandez-Marcos PJ, Auwerx J. Regulation of PGC-1α, a nodal regulator of mitochondrial biogenesis. The American journal of clinical nutrition. 2011;93(4):884S-90.
132. Kuo YT, Shih PH, Kao SH, et al. Pyrroloquinoline Quinone Resists Denervation-Induced Skeletal Muscle Atrophy by Activating PGC-1α and Integrating Mitochondrial Electron Transport Chain Complexes. PLoS One. 2015;10(12):e0143600.
133. He K, Nukada H, Urakami T, et al. Antioxidant and pro-oxidant properties of pyrroloquinoline quinone (PQQ): implications for its function in biological systems. Biochem Pharmacol. 2003 Jan 1;65(1):67-74.
134. Lu J, Chen S, Shen M, et al. Mitochondrial regulation by pyrroloquinoline quinone prevents rotenone-induced neurotoxicity in Parkinson's disease models. Neurosci Lett. 2018 Nov 20;687:104-110.
135. Chowanadisai W, Bauerly KA, Tchaparian E, et al. Pyrroloquinoline quinone stimulates mitochondrial biogenesis through cAMP response element-binding protein phosphorylation and increased PGC-1alpha expression. The Journal of biological chemistry. 2010;285(1):142-152.
136. Saihara K, Kamikubo R, Ikemoto K, et al. Pyrroloquinoline Quinone, a Redox-Active o-Quinone, Stimulates Mitochondrial Biogenesis by Activating the SIRT1/PGC-1α Signaling Pathway. Biochemistry. 2017 Dec 19;56(50):6615-6625.

137. Tinggi U. Selenium: its role as antioxidant in human health. Environmental health and preventive medicine. 2008;13(2):102-108.
138. Mendelev N, Mehta SL, Idris H, et al. Selenite Stimulates Mitochondrial Biogenesis Signaling and Enhances Mitochondrial Functional Performance in Murine Hippocampal Neuronal Cells. PLOS ONE. 2012;7(10):e47910.
139. Du K, Montminy M. CREB is a regulatory target for the protein kinase Akt/PKB. J Biol Chem. 1998 Dec 4;273(49):32377-9.
140. Mehta SL, Kumari S, Mendelev N, et al. Selenium preserves mitochondrial function, stimulates mitochondrial biogenesis, and reduces infarct volume after focal cerebral ischemia. BMC neuroscience. 2012;13:79-79.
141. Mangiapane E, Pessione A, Pessione E. Selenium and selenoproteins: an overview on different biological systems. Curr Protein Pept Sci. 2014;15(6):598-607.
142. Oliveira-Silva JA, Yamamoto JUP, Oliveira RB, et al. Oxidative stress assessment by glutathione peroxidase activity and glutathione levels in response to selenium supplementation in patients with Mucopolysaccharidosis I, II and VI. Genet Mol Biol. 2019 Jan-Mar;42(1):1-8.
143. Hargreaves IP, Mantle D. Supplementation with selenium and coenzyme Q10 in critically ill patients. Br J Hosp Med (Lond). 2019 Oct 2;80(10):589-593.
144. Xia L, Nordman T, Olsson JM, et al. The mammalian cytosolic selenoenzyme thioredoxin reductase reduces ubiquinone. A novel mechanism for defense against oxidative stress. J Biol Chem. 2003 Jan 24;278(4):2141-6.
145. Moosmann B, Behl C. Selenoproteins, cholesterol-lowering drugs, and the consequences: revisiting of the mevalonate pathway. Trends Cardiovasc Med. 2004 Oct;14(7):273-81.
146. Malapaka RRV, Khoo S, Zhang J, et al. Identification and mechanism of 10-carbon fatty acid as modulating ligand of peroxisome proliferator-activated receptors. The Journal of biological chemistry. 2012;287(1):183-195.
147. Liang H, Ward WF. PGC-1α: a key regulator of energy metabolism. Advances in Physiology Education. 2006;30(4):145-151.
148. Kanabus M, Fassone E, Hughes SD, et al. The pleiotropic effects of decanoic acid treatment on mitochondrial function in fibroblasts from patients with complex I deficient Leigh syndrome. Journal of inherited metabolic disease. 2016;39(3):415-426.
149. Hughes SD, Kanabus M, Anderson G, et al. The ketogenic diet component decanoic acid increases mitochondrial citrate synthase and complex I activity in neuronal cells. J Neurochem. 2014 May;129(3):426-33.
150. Greco T, Glenn TC, Hovda DA, et al. Ketogenic diet decreases oxidative stress and improves mitochondrial respiratory complex activity. Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism. 2016;36(9):1603-1613.
151. Hasan-Olive MM, Lauritzen KH, Ali M, et al. A Ketogenic Diet Improves Mitochondrial Biogenesis and Bioenergetics via the PGC1α-SIRT3-UCP2 Axis. Neurochem Res. 2019 Jan;44(1):22-37.
152. Ford S, O'Driscoll M, MacDonald A. Living with Phenylketonuria: Lessons from the PKU community. Molecular genetics and metabolism reports. 2018;17:57-63.
153. Robert M, Rocha JC, van Rijn M, et al. Micronutrient status in phenylketonuria. Molecular Genetics and Metabolism. 2013 2013/01/01/;110:S6-S17.
154. Liguori I, Russo G, Curcio F, et al. Oxidative stress, aging, and diseases. Clinical interventions in aging. 2018;13:757-772.
155. Plotegher N, Duchen MR. Mitochondrial Dysfunction and Neurodegeneration in Lysosomal Storage Disorders. Trends in Molecular Medicine. 2017;23(2):116-134.
156. Yambire KF, Fernandez-Mosquera L, Steinfeld R, et al. Mitochondrial biogenesis is transcriptionally repressed in lysosomal lipid storage diseases. eLife. 2019 2019/02/18;8:e39598.

157. Ivankovic D, Chau KY, Schapira AH, et al. Mitochondrial and lysosomal biogenesis are activated following PINK1/parkin-mediated mitophagy. J Neurochem. 2016 Jan;136(2):388-402.
158. Zhou X, Yang J, Zhou M, et al. Resveratrol attenuates endothelial oxidative injury by inducing autophagy via the activation of transcription factor EB. Nutrition & Metabolism. 2019 2019/07/02;16(1):42.
159. Csiszar A, Labinskyy N, Pinto JT, et al. Resveratrol induces mitochondrial biogenesis in endothelial cells. American journal of physiology Heart and circulatory physiology. 2009;297(1):H13-H20.