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REVIEW

This paper is dedicated to the 70th anniversary of the founding of Physiologia Bohemoslovaca (currently Physiological Research)

Coenzyme Q_{10} Effects in Neurological Diseases

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Summary

Coenzyme Q_{10} (CoQ_{10}), a lipophilic substituted benzoquinone, is present in animal and plant cells. It is endogenously synthetized in every cell and involved in a variety of cellular processes. CoQ_{10} is an obligatory component of the respiratory chain in inner mitochondrial membrane. In addition, the presence of CoQ_{10} in all cellular membranes and in blood. It is the only endogenous lipid antioxidant. Moreover, it is an essential factor for uncoupling protein and controls the permeability transition pore in mitochondria. It also participates in extramitochondrial electron transport and controls membrane physicochemical properties. CoQ_{10} effects on gene expression might affect the overall metabolism. Primary changes in the energetic and antioxidant functions can explain its remedial effects. CoQ_{10} supplementation is safe and well-tolerated, even at high doses. CoQ_{10} does not cause any serious adverse effects in humans or experimental animals. New preparations of CoQ_{10} that are less hydrophobic and structural derivatives, like idebenone and MitoQ, are being developed to increase absorption and tissue distribution. The review aims to summarize clinical and experimental effects of CoQ_{10} supplementations in some neurological diseases such as migraine, Parkinson´s disease, Huntington´s disease, Alzheimer´s disease, amyotrophic lateral sclerosis, Friedreich´s ataxia or multiple sclerosis. Cardiovascular hypertension was included because of its central mechanisms controlling blood pressure in the brainstem rostral ventrolateral medulla and hypothalamic paraventricular nucleus. In conclusion, it seems reasonable to recommend CoQ_{10} as adjunct to conventional therapy in some cases. However, sometimes CoQ_{10} supplementations are more efficient in animal models of diseases than in human patients (e.g. Parkinson´s disease) or rather vague (e.g. Friedreich´s ataxia or amyotrophic lateral sclerosis).

Key words

Idebenone • MitoQ • Migraine • Parkinson´s disease • Alzheimer´s disease • Multiple sclerosis • Hypertension

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Introduction

Coenzyme Q (CoQ), a highly hydrophobic molecule, is known from 1957 when it was isolated from beef heart mitochondria by Professor Frederick Crane on Madison University (Crane *et al.* 1957, Crane 1989). CoQ is composed of a benzoquinone ring and a polyisoprenoid lipid tail containing varying chain length depending on the species (Fig. 1). Human isoform contains ten isoprene units (CoQ_{10}) but rodents have mainly nine units (CoQ_9) besides some amount of CoQ_{10}. Briefly, the benzoquinone ring is derived from the essential amino acid phenylalanine, which is converted into tyrosine and then 4-hydroxybenzoate. The polyisoprenoid lipid tail subunits are generated from acetyl-CoA (and through joint intermediate of cholesterol – farnesyl-pyrophosphate) by the mevalonate pathway. The last phase of a CoQ biosynthesis is the condensation of the benzoquinone ring and the polyisoprenoid tail. A lot of knowledge on CoQ biosynthesis originated from experiments on simple organisms such as the budding yeast *Saccharomyces cerevisia*, fission yeast *Schizosaccharomyces plombe* or coliform bacterium

Escherichia coli etc. (Awad *et al.* 2018, Wang and Hekimi 2013). Stefely and Pagliarini (2017) summarized the recent progress and defined still existing knowledge gaps in CoQ biosynthesis.

CoQ is present in most aerobic organisms, all animal and plant organs (Battino *et al.* 1990, Elmberger *et al.* 1987, Ramasarma 1985). It is endogenously produced in every cell and its intracellular synthesis is its major source, although a small proportion is acquired through the diet. Meat, fish, nuts, and some oils are the richest nutritional sources of CoQ, while much lower levels can be found in most dairy products, vegetables, fruits, and cereals (Cabrini *et al.* 2001, Kamei *et al.* 1986, Kettawan *et al.* 2007, Pravst *et al.* 2010, Pyo 2010). Interestingly, the daily intake in different countries is very similar and represents around 3-5 mg (Kubo *et al.* 2008, Mattila and Kumpulainen 2001, Weber *et al.* 1997a,b).

CoQ concentrations are modified in humans and rats during lifespan (Beyer *et al.* 1985, Kalén *et al.* 1989, Zhang *et al.* 1996). Although the results of the various studies are not in total agreement, generally, in the early phase of life, CoQ concentrations increase, whereas during aging they decrease. Wada *et al.* (2007) demonstrated that not only the amount of CoQ but also its redox status is essential to balance the oxidative stress

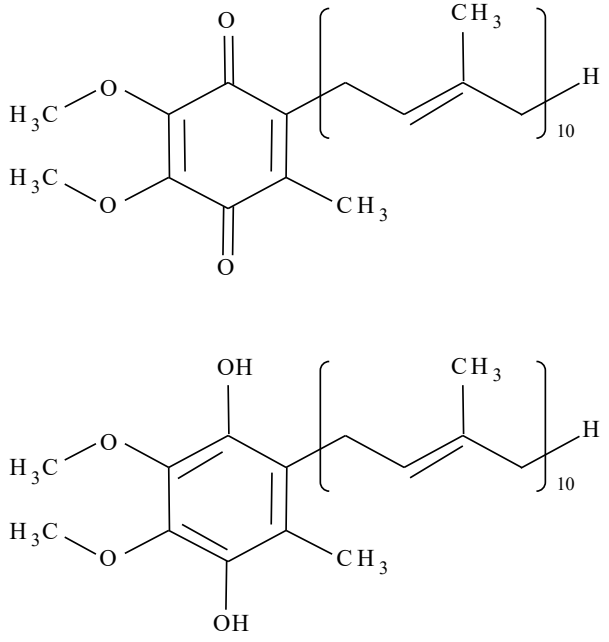

Fig. 1. Chemical structure composed from benzoquinone head and hydrophobic polyisoprenoid tail of fully reduced (ubiquinol, bottom) and fully oxidized (ubiquinone, top) forms of human derivative of coenzyme Q_{10} (CoQ_{10})

associated with the aging process. CoQ concentrations also decrease in mice and pigs with the age. Similarly, an oxidized form of CoQ_{10} increases indicating higher oxidative stress or a decreased anti-oxidative capacity of aged animals (Onur *et al.* 2014). Battino *et al.* (1995) described in rats that CoQ_9 and CoQ_{10} contents in different mitochondrial fractions (synaptic and non-synaptic) are slowly decreasing in three brain areas (cortex, striatum and hippocampus), reaching their minimum in age of 18 months, then increased in the older rats. Nevertheless, the CoQ_9/CoQ_{10} ratio remained constant during aging.

Apart from the earlier study by Kalén *et al.* (1989) there are few recent human trials. A large cohort of 860 European adults aged 18-82 years shows a decrease of CoQ_{10} blood concentrations with a shift in redox status in favour of the oxidized fraction in old people of both sexes (Nicklowitz *et al.* 2016). The recent study on Japanese centenarians (25 males and 74 females) compared to 76-year-old controls confirms decreased serum total levels of CoQ_{10} significantly shifted to the oxidized form (Nagase *et al.* 2018). Thus, exogenous CoQ_{10} supplementation may show benefits as an antiaging agent during aging process.

Subjects are not generally dependent on exogenous supplies of CoQ_{10}. However, apart ageing CoQ_{10} concentrations are also affected during different pathological disorders. Under these circumstances, dietary supplementation may be needed and would fulfill important functions by counteracting CoQ_{10} depletion. Most of the clinical work with CoQ_{10} is focused on the wide spectrum of heart diseases such as ischemic heart disease, congestive heart failure or different cardiomyopathies (Rauchová and Vokurková 2009).

In this short review I have attempted to show the changes of CoQ_{10} content in different diseases and possible brain effects of the treatment with CoQ_{10} (and its derivatives) supplementation. This review is focused on CoQ_{10} applications in CoQ_{10} deficiency, very frequent type of headache – migraine – and other nervous diseases (Parkinson´s disease, Alzheimer´s diseases, Friedreich´s ataxia or Huntington disease, amyloid lateral sclerosis, sclerosis multiplex) and improvement in noice-induced hearing loss or in cardiovascular hypertension control.

Multiple functions of coenzyme Q

CoQ, also known as ubiquinone, acts as a mobile electron and proton transporter from complex I (NADH:

ubiquinone reductase) and complex II (succinate: ubiquinone reductase) to complex III (ubiquinone cytochrome *c* oxidase) in the inner mitochondrial membrane (Trumpower 1981). The subcellular distribution shows that the inner mitochondrial membrane has the largest portion of CoQ. In comparison with other respiratory carriers the content of CoQ exceeds other redox components by about tenfold (Capaldi 1982). Moreover, CoQ accepts electrons from other dehydrogenases, which are present in lower amounts, and seems to be rate-limiting in the integrated electron transfer (Genova and Lenaz 2011, 2014). Among them localized on the outer surface of the inner membrane there is mitochondrial FAD-linked glycerol-3-phosphate dehydrogenase – the simplest branch of the respiratory chain and a part of glycerol-3-phosphate shuttle (Rauchová *et al.* 1992, Rauchová *et al.* 1997). CoQ is also an obligatory cofactor for FMN-linked dihydroorotate dehydrogenase – a key enzyme of *de novo* pyrimidine biosynthesis, which is loosely associated with the outer surface of the inner membrane (Evans and Guy 2004, Reis *et al.* 2017). On the matrix side of inner membrane there is electron transport flavoprotein dehydrogenase forming a short pathway that transfer electron from 11 different mitochondrial flavoprotein dehydrogenases to the quinone pool – an essential enzyme involved in the fatty acid β-oxidation and branched-chain amino acid oxidation pathways (Frerman 1988, Watmough and Frerman 2010). Further there are FAD-dependent proline dehydrogenase (an enzyme required for proline and arginine metabolism) and sulphide-quinone oxidoreductase (Blake *et al.* 1976, Quinzii *et al.* 2017). Fig. 2 shows a schematic illustration of the CoQ integration in the mammalian mitochondrial respiratory chain.

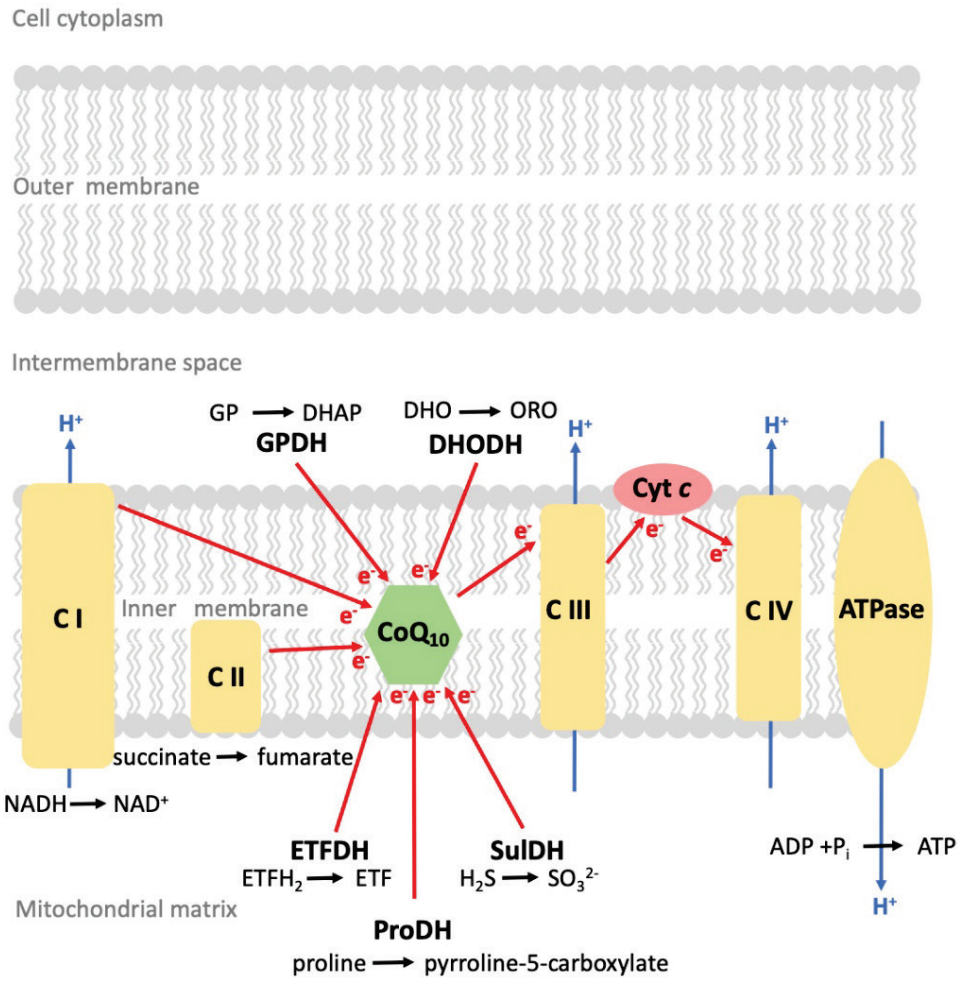

Fig. 2. A schematic illustration of CoQ_{10} intergration in the mammalian mitochondrial respiratory chain. Electrons (e-) accept oxidized form of coenzyme Q_10 (CoQ_{10}) from complex I (C I) and complex II (C II), mitochondrial glycerol-3-phosphate dehydro-genase (GPDH), dihydroorotate dehydro-genase (DHODH), electron transport flavoprotein dehydro-genase (ETFDH), proline dehydrogenase (ProDH) and sulfide dehydro-genase (SulDH) for delivery to complex III (C III) and finally to complex IV (C IV). Glycerol-3-phosphat (GP), dihydroxyaceton phosphate (DHAP), dihydroorotate (DHO), orotate (ORO), cytochrome c (Cyt c)

Beyond fundamental role of an electron carrier associated with cellular energy production in the respiratory chain, CoQ functions as a principal cofactor in the activation of protein uncoupling (Echtay *et al.* 2000) and it controls permeability of transition pores (Fontaine *et al.* 1998, Walter *et al.* 2002). However, CoQ occurs in other cellular membranes such as Golgi apparatus, lysosomes or plasma membrane having a role in functioning of oxido-reductase systems. Gille and Nohl (2000) described the lysosomal membrane redox chain, which provides the low pH inside the organel for the best functioning hydrolytic enzymes necessary for the removal of useless proteins. Moreover, CoQ can also change membrane stability or fluidity what could be important for physiological functions of receptors, carriers and membrane-bound enzymes (Agmo Hernández *et al.* 2015, Fato *et al.* 1984). The bioinformatic analyses show that CoQ affects the expression of many genes involved in different cellular pathways (Schmelzer *et al.* 2007).

In addition, CoQ turns between fully oxidized form, quinone, – through a formation of its semiquinone – and fully reduced form (Fig. 1). The reduced form, ubiquinol, functions as a potent antioxidant and free radical scavenger by either directly scavenging free radicals or recycling and regenerating other antioxidants such as tocopherol (vitamin E) and ascorbic acid (vitamin C). So, by this way it protects membrane lipids, proteins and mitochondrial DNA against oxidative damage. CoQ represents the only lipid soluble antioxidant synthesized by own cells. On the other hand, oxido-reduction character of CoQ has also the important prooxidant role for the formation of superoxide anion (O_2^-) and hydrogen peroxide (H_2O_2) in cell signaling systems (Linnane *et al.* 2007). Furthermore, CoQ acts as a regulator of cell growth and differentiation and a blocker of apoptosis (Kagan *et al.* 1999, Li *et al.* 2019) and has anti-inflammatory effects (Schmelzer *et al.* 2007, Schmelzer *et al.* 2008). Systematic reviews evaluated the effects of CoQ_{10} supplementation on various inflammatory markers including C-reactive protein, interleukin-6 or tumor necrosis factor-α (Fan *et al.* 2017, Zhai *et al.* 2017).

The functional diversity reflects a suitability of CoQ for applications in clinical studies as an alternative medication or dietary supplement for several diseases, which also includes neurological disorders.

Safety and bioavailability of coenzyme Q_{10}

As a natural component, CoQ_{10} is well tolerated. However, its therapeutic applications are greatly limited because CoQ_{10} is almost insoluble in water (due to its high hydrophobicity) and has relatively large molecular mass (863.34 g/mol). In rats, only about 2-4 % of orally administered CoQ_{10} could be absorbed (Zhang *et al.* 1995). Divided dosages (2 x100 mg) produce a larger increase in plasma levels than a single peroral 200 mg dose (Singh *et al.* 2005). Hence, large daily doses are recommended to be divided into several doses to maximize the CoQ_{10} absorption. To improve its solubility and bioavailability, several advancements have been made and a variety of preparations has been developed such as compressed tablets, chewable tablets, powder-filled capsules or soft gels containing a suspension in oil (Bhagavan and Chopra 2007). Very recent papers summarize data about various preparations of CoQ_{10} with improved solubility and biological availability (Ehrenhaus Masotta *et al.* 2020, Pastor-Maldonado *et al.* 2020, Pravst *et al.* 2020, Takahashi and Takahashi 2019). Water-soluble CoQ_{10} that improves the bioavailability of natural CoQ_{10} is non-toxic and stable over long periods of time Ubisol-Q_{10} prepared by method using polyethylene glycol-derivatised natural compounds (Borowy-Borowski *et al.* 2004).

Orally administered CoQ_{10} is absorbed from the gastrointestinal tract (GIT) similarly as vitamin E or different lipid soluble substances (Bhagavan and Chopra 2007). The data disclosed regional differences in permeability throughout the GIT (Palamakula *et al.* 2005). The maximum permeability occurred in the duodenum pointing at the peculiar expression of transporters along the GIT. The second most favorable region for absorption was the colon followed by the jejunum and stomach. After the absorption in GIT, CoQ_{10} is reduced and transported to the liver, where it is incorporated into chylomicrons. In the circulation CoQ_{10} is transported as very low-density lipoprotein (VLDL) or low-density lipoprotein (LDL) particles. After oral administration, the maximum plasma CoQ_{10} concentration occurs at 6 to 8 hours (Bhagavan and Chopra 2006). Ochiai *et al.* (2007) found that intestinal absorption of CoQ_{10} after administration of the emulsion formulation of CoQ_{10} was also enhanced by food intake in Wistar rats: intestinal absorption was three times faster with food intake. However, the large interindividual variations following the CoQ_{10} administration were

demonstrated. Mantle and Dybring (2020) summarized that the relative bioavaibility and efficacy of administered oxidized and reduced forms of CoQ_{10} seems to be similar. Moreover, various cell types lining the GIT may have a capacity to reduce CoQ_{10} and facilitate its conversion. Evidence from pharmacokinetic studies suggest that exogenous supplementation of CoQ_{10} does not influence the biosynthesis of endogenous CoQ_9/CoQ_{10} nor does it accumulate in plasma or tissues after the cessation of supplementation (Hidaka *et al.* 2008).

As concerns CoQ_{10} crossing brain capillary endothelial cells i.e. the blood-brain barrier (BBB) Matthews *et al.* (1998) showed that oral administration of CoQ_{10} (200 mg/kg/day for two months) increased both brain and brain mitochondrial concentrations in 12- and 24-month-old male Sprague-Dawley or 24-month-old Fisher 344 rats. Kwong *et al.* (2002) reported small but significant increase in brain mitochondria in 14-month-old male Sprague-Dawley for 13 weeks feeding (150 mg/kg/day). Smith *et al.* (2006) used high doses (1,000-5,000 mg/kg/day) of CoQ_{10} in the R6/2 transgenic mouse model of Huntington's disease and significantly increased plasma and brain levels of CoQ_{10} and CoQ_9. Kamzalov *et al.* (2003) found significantly elevated CoQ_{10} in brain mitochondria but not in the brain homogenate in male mouse C57B1 for 11 weeks feeding. On the other hand, other reports show no increase of CoQ_{10} with oral administration in 3-month-old or 24-month-old male C57B1 mouse or C65/B16 (Lass *et al.* 1999, Sohal *et al.* 2006, Wadsworth *et al.* 2008).

CoQ_{10} (30 mg/kg) crossed BBB of adult male Wistar rats and accumulated in the brain when administered intravenously (Belousova *et al.* 2016). A single intravenous injection of CoQ_{10} in the rat model of transient focal ischemia led to a 67 % reduction in brain lession size 24 hours after CoQ_{10} administration and although the infarct had increased by 7 days, it remained smaller than that of saline-treated rats (Belousova *et al.* 2016). Recently, Wainwright *et al.* (2020) investigated mechanisms of CoQ_{10} transport across the BBB, using normal and pathophysiological (CoQ_{10}-deficient) cell culture models and identified lipoprotein-associated uptake and efflux mechanisms regulating CoQ_{10} transfer. They showed that there is a dynamic interplay of multiple transport receptors with varying degrees of influence. They brought a substantial evidence for the involvement of receptor for advanced glycation endproducts, low density lipoprotein receptor and scavenger receptor in the transport of exogenous CoQ_{10} into brain.

CoQ_{10} is well tolerated and safe. Data from experimental and clinical studies indicated repeatedly that CoQ_{10} is highly safe for the use as a dietary supplement compared with placebo group (Ferrante *et al.* 2005, Huntington Study Group Pre2CARE Investigators *et al.* 2010, Kitano *et al.* 2008, Liu and Artmann 2009, Zhu *et al.* 2017). Kitano *et al.* (2008) evaluated the potential subchronic toxicity of reduced and oxidized CoQ_{10} orally administered to Sprague-Dawley rats (rodents with the primary form of CoQ_9) and beagle dogs (mammals with the primary form of CoQ_{10}). The authors observed no adverse effects in male or female rats administered 600 and 200 mg/kg/day, respectively. In the dog study, the highest dose tested (600 mg/kg/day) indicated no adverse effects in males and females. The observed safe level risk assessment method indicated that the evidence of safety is strong at intakes up to 1,200 mg/day (Hathcock and Shao 2006, Ikematsu *et al.* 2006). Nevertheless, even a daily dosage up to 3,600 mg was found to be tolerated by healthy as well as unhealthy persons (Huntington Study Group Pre2CARE Investigators *et al.* 2010). In general, CoQ_{10} shows only a low incidence of adverse events: dizziness, nausea/vomiting, heartburn, stomach upset or related mild and transient gastrointestinal effects (Hathcock and Shao 2006, Raizner 2019).

It should be noted that CoQ_{10} is not approved by the US Food and Drug Administration for treatment of any medical condition (Raizner 2019). It is sold as a food additive, not as drugs, and its manufacturing is not regulated in the same way as drugs. The European Medicine Agency approved ubiquinol ─ the reduced form of CoQ_{10} ─ as an orphan drug for the treatment of primary CoQ_{10} deficiency in 2016. According to my knowledge, Myoquinon (Pharma Nord ApS) is approved for medical treatment of proven CoQ_{10} deficiency or adjunctive therapy to relieve symptoms of chronic heart failure in Hungary.

Coenzyme Q_{10} analogues

A synthetic short-chain analogue of CoQ_{10} idebenone (hydroxydecylubiquinone, IDB) was launched by Japanese Takeda Chemical Industries in 1986 (Fig. 3). IDB with a hydroxydecyl side chain (10 carbon atoms) and m.w. 339.44 is less hydrophobic than natural CoQ_{10} with m.w. 863.49 (Zs-Nagy et al. 1990). IDB acts as an electron carrier in the mitochondrial electron transport chain but it inhibits complex I – NADH dehydrogenase (Esposti *et al.* 1996, Rauchová *et al.* 2008). On the other

hand, IDB transfers electrons from complex II – succinate dehydrogenase or from glycerol-3-phosphate dehydrogenase to complex III (Brière *et al.* 2004, Rauchová *et al.* 2012). Similarly, as CoQ_{10}, IDB acts as a potent antioxidant agent (Lin *et al.* 2015, Muscoli *et al.* 2002, Rauchová *et al.* 2006). IDB is well-tolerated in experiments and clinical trials, e.g. for patients with Friedreich´s ataxia, Huntington´s disease, Alzheimer´s disease, multiple sclerosis etc. (Jaber and Polster 2015). To improve IDB effectiveness in the therapeutic treatment, IDB similarly to CoQ_{10} can be incorporated in liposomes, cyclodextrins or nanoparticles (Montenegro *et al.* 2018). Gueven *et al.* (2015) compared the structural similarity, pharmacokinetics and modulation of cellular energy production of IDB and natural CoQ_{10}. Consequently, IDB and CoQ_{10} are unable to substitute for each other. A very recent review of Gueven *et al.* (2021) summarized that IDB (and its metabolites) protect against the multitude of toxic stimuli. The authors also mentioned some new discoveries e.g., competitive inhibition of p52Shc, retinal expression of the RNA-binding protein Lin28A or impact on inflammation and endoplasmatic reticulum stress. Thus, the effects of IDB cannot be explained only by an antioxidant activity or a normalization of mitochondrial energy supply. It seems more likely that IDB activates one or several essential pathways that explain its broad activity (Gueven *et al.* 2021). A broad range of IDB activity is very similar to multiple functions of coenzyme Q but the activities might also be different because of different chemical structure.

Mitoquinone (MitoQ) was developed for oxidative stress treatment (James *et al.* 2005, Smith and Murphy 2010). Structure of MitoQ consists of lipophilic cation ─ triphenylphosphonium (TPP) attached to ubiquinone head group via a 10-carbon aliphatic chain (Fig. 4). MitoQ crosses easily through all biological membranes, including the blood-brain barrier and neuronal membranes. MitoQ concentrates hundredfolds in mitochondria driven by high membrane potential across the inner mitochondrial membrane. Oral delivery of MitoQ protects mitochondria from damage and may therefore form the basis for mitochondria-protective therapies (Murphy and Smith 2007). It was shown that MitoQ had a protective role in animal and cell models of several human disease, including Parkinson's disease, Alzheimer's disease or sclerosis multiplex.

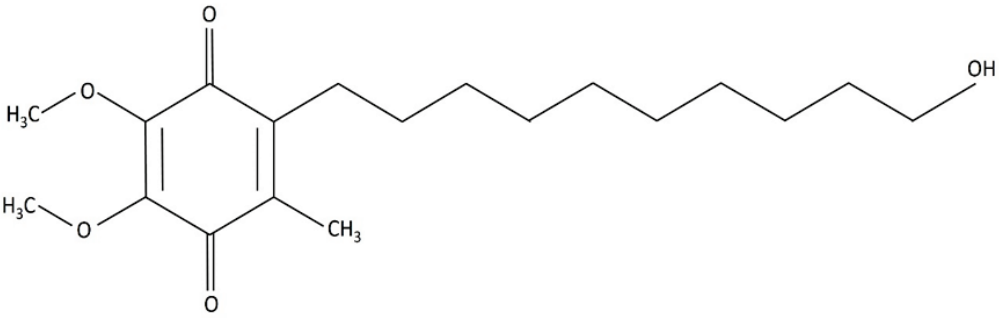

Fig. 3. Chemical structure of synthetic analogue of CoQ_{10}, idebenone with only 10 carbons in its aliphatic side chain

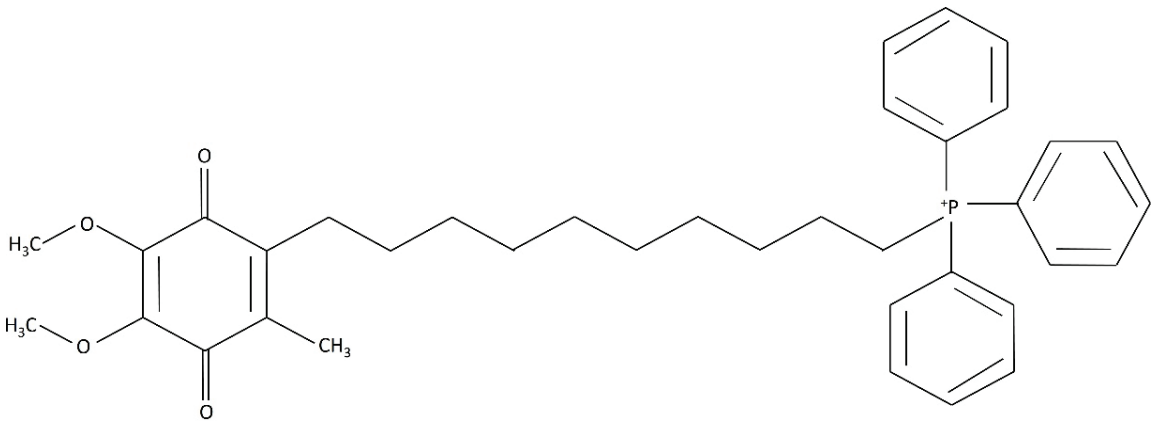

Fig. 4. Chemical structure of MitoQ

CoQ_{10} deficiency

Primary CoQ_{10} deficiency, which can cause reduced levels of CoQ_{10} in tissues, includes mutations in the genes participating in the complicated biosynthesis of CoQ_{10}, as described by Mollet *et al.* (2007), Ogasahara *et al.* (1989), Quinzii *et al.* (2006), Rötig *et al.* (2000) and others. In many cases the family history suggests an autosomal recessive mode of inheritance. Alzár-Fabra *et al.* (2018) presented the updated comprehensive review of the very heterogeneous clinical spectrum associated with primary CoQ_{10} deficiency. At present 10 genes encoding biosynthesis of CoQ_{10} have their pathogenic variants bringing about human CoQ_{10} deficiency (Alzár-Fabra *et al.* 2018). Besides of cardiac, muscular and renal manifestations the peripheral and central nervous system is often affected including encephalopathy, seizures, cerebellar ataxia, epilepsy, sensorineural hearing loss, optic atrophy or intellectual disability in these patients.

Primary CoQ_{10} deficiency is very rare (Yu *et al.* 2019). Much more frequent secondary CoQ_{10} deficiency includes the defects not directly connected with biosynthesis of CoQ_{10} (Alzár-Fabra *et al.* 2018, Desbats *et al.* 2015, Yubero *et al.* 2016). Many reports focus on skeletal muscle and central nervous system. Muscular manifestations consist of weakness, hypotonia, exercise intolerance and myoglobinuria, while the main CNS manifestations include ataxia and general CNS impairment (Desbats *et al.* 2015).

CoQ_{10} suplementation can be effective for treatment of both primary and secondary CoQ_{10} deficiencies (Potgieter *et al.* 2013). Duberley *et al.* (2014) evaluated the effect of CoQ_{10} supplementation on the well-established neuronal model of CoQ_{10} deficiency. Human SH-SY5Y neuronal cells with 1 mM competitive inhibitor of mammalian CoQ biosynthesis in cell cultures ─ para-aminobenzoic acid ─ induced approximately a half decrease of cellular CoQ_{10} concentration accompaining by a fourfold increase in mitochondrial oxidative stress and global loss of mitochondrial respiratory chain enzyme activities. Following CoQ_{10} supplementation for 5 days there was a markedly increased cellular CoQ_{10} status. CoQ_{10} treatment (2.5 μM) significantly decreased the level of mitochondrial superoxide in the CoQ_{10}-deficient neurons. CoQ_{10} treatment (5 μM) restored mitochondrial membrane potential to 90 % of the control level. However, CoQ_{10} treatment (10 μM) was only partially effective in restoring enzyme activities of mitochondrial respiratory chain. This study indicated that although mitochondrial oxidative stress can be attenuated in CoQ_{10}-deficient neurons following CoQ_{10} supplementation, mitochondrial respiratory chain enzyme activities appear to be partially refractory to this treatment. The therapy with >10 μM CoQ_{10} may be required to restore mitochondrial respiratory chain enzyme activities to the control level.

Very important for the treatment of primary or secondary CoQ_{10} deficiency is early identification and early supplementation to omit irreversible damages in the central nervous system (and other organs).

Migraine

Migraine is a debilitaiting condition characterized by headaches and nausea with a usual onset around puberty. Associated symptoms may be sensitivity to light, sound or smell and vomiting. Migraine affects 10 % people worldwide and it is approximately three times more common in women than in men (Vos *et al.* 2012, Woldeamanuel and Cowan 2017). Although migraine ranks among the most frequent neurological disorders, its pathophysiology remains not fully understood. Mitochondria and energetic metabolism have long been postulated to be involved in the etiology of migraines, although a direct link has been difficult to identify (Sparaco *et al.* 2006, Yorns and Hardison 2013).

A small open-label study with 32 adults showed some effectiveness of 150 mg of CoQ_{10} supplementation as a preventive treatment for migraine headaches (Rozen *et al.* 2002). The other (double-blind, randomized, placebo-controlled) study with 42 adult migraine patients used CoQ_{10} supplementation (3x100 mg/day). CoQ_{10} was superior to placebo for attack frequency, headache-days and days-with-nausea in the third treatment month (Sándor *et al.* 2005).

Hershey *et al.* (2007) found that deficiency of CoQ_{10} may be quite common in pediatric and adolescent migraine. They measured plasma CoQ_{10} in 1550 patients (aged 13 to 22 years). Consequent CoQ_{10} supplementation in patients with low plasma CoQ_{10} (1 to 3 mg/kg/day of CoQ_{10} in liquid gel capsule formulation) resulted in clinical improvement. In a double-blinded, placebo-controled study with 120 pediatric and adolescent migraine receiving 100 mg CoQ_{10} supplementation for 32 weeks, the improvement was seen in weeks 1-4 but there was no difference in headache outcomes between the CoQ_{10} supplementation and

placebo in week 32 (Slater *et al.* 2011). CoQ_{10} supplementation (400 mg/day per 3 months together with prophylactic medication) showed significant improvement in frequency, severity and duration of migraine attacks in CoQ_{10} group compared to placebo in 45 women aged 18-50 years. Interestingly, the levels of inflammatory marker tumor necrosis factor-α (TNF-α) were reduced significantly but interleukin IL-6 and IL-10 levels were not affected (Dahri *et al.* 2019).

Recently, Zeng *et al.* (2019) included five studies from 2002-2018 with 346 patients (120 pediatric and 226 adult subjects) in the meta-analysis. CoQ_{10} was comparable with placebo in respect to migraine attacks/month and migraine severity/day. However, CoQ_{10} was more effective than placebo in reducing migraine days/month and migraine duration. Another recent meta-analysis included four studies from 2005-2018 with 221 patients (Parohan *et al.* 2020). They concluded that the greatest impact of CoQ_{10} supplementation was on the frequency of attacts per month without affecting the severity or duration of migraine attacks.

In addition to CoQ_{10} several other nutraceuticals have been demonstrated to have potential effectiveness for migraine prevention such as magnesium, riboflavin, carnitine or herbal remedies and their different combinations together with aerobic exercise or other forms of relaxation training, cognitive therapies and acupuncture (Mauskop 2012). A double-blind, placebo-controled study with 130 adult patients (18-65 years) evaluated the efficacy of a proprietary supplement containing magnesium, riboflavin and Q_{10} (commercially available food supplement Migravent® in Germany or Dolovent® in USA) (Gaul *et al.* 2015). After three months of treatment with this supplement, a pain and burden of migraine were statistically significantly reduced compared to placebo patients, but it did not show statistically significant efficacy on migraine frequency. Results with another proprietary supplement containing feverfew *(Tanacetum parthenium)*, CoQ_{10} and magnesium (Antemig® in France since 2014) could be beneficial and safe for the prevention of migraine in adult patients (Guilbot *et al.* 2017). A double-blind 8-week lasting study with concurrent CoQ_{10} (30 mg/day) and carnitine (500 mg/day) supplementation provided the evidence supporting some beneficial effects on mitochondrial metabolism (decrease of lactate serum level) and migraine symptoms (Hajihashemi *et al.* 2019). Parohan *et al.* (2021) reported a synergistic effect of nano-curcumin and CoQ_{10} (300 mg/day) given for 8 weeks in a double-blind, placebo-controled study with 91 adult patients.

Parkinson´s disease

Parkinson´s disease (PD) is one of the most common neurodegenerative diseases with still unknown primary cause. There is a long-term degenerative disorder of the central nervous system that mainly affects the motor system and affects about 1-2 % of the elderly population with usual onset over 60. It is prevalent in males. The most obvious symptoms are shaking (due to decrease in dopaminergic modulation of the substantia nigra pars compacta neurons altering motor systems), rigidity, slowness of movement and difficulty with walking. Inclusions of Lewy bodies in midbrain and presence of immunoreactive α-synuclein and ubiquitin on autopsy are hallmarks of the disease (Oertel and Schulz 2016, Stanga *et al.* 2020). Mitochondrial dysfunction contributes significantly to neuronal loss in PD (McCoy and Cookson 2012, Stanga *et al.* 2020). Mitochondria of patients have decreased complex I activity not only in substantia nigra (Schapira *et al.* 1990a, b), striatum (Mizuno *et al.* 1989) and frontal cortex (Parker *et al.* 2008) but also in skeletal muscle (Bindoff *et al.* 1991) or platelets (Haas *et al.* 1995, Krige *et al.* 1992). The other study found significant deficiency of CoQ_{10} in cortex but not in substantia nigra, striatum or cerebellum in brains samples of PD patients (Hargreaves *et al.* 2008). Studies also reported deficiency of CoQ_{10} platelets (Krige *et al.* 1992, Shults *et al.* 1997). Functional intracellular assay (FIA) methodology analyzing blood samples also assessed CoQ_{10} deficiency in patients with PD compared to age- and gender-matched controls (Mischley *et al.* 2012). In addition, their mitochondria show oxidative stress, disturbance in calcium homeostasis, impaired clearance of dysfunctional mitochondria, changes in mitochondrial biogenesis and the loss of membrane potential (McCoy and Cookson 2012).

Inhibitors of mitochondrial complex I of the oxidative phosphorylation pathway induce degeneration of dopaminergic neurotransmission in rodents and several other animal models of PD (Hamadjida *et al.* 2019, Tieu 2011). The most often used chemicals are MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (Beal *et al.* 1998, Jackson-Lewis and Przedborski 2007, Przedborski *et al.* 2004), nonselective herbicide paraquat (PQ), N,N'-dimethyl-4-4'-bipiridinium (Cicchetti *et al.* 2005,

McCarthy *et al.* 2004), or botanical insecticide and nonselective piscicide rotenone (Caboni *et al.* 2004, Cannon *et al*. 2009, Sherer *et al*. 2003). Many scientists found some benefit of CoQ_{10} supplementation in the above-mentioned experimental animal models of PD. Cleren *et al.* (2008) showed significant neuroprotective effects of CoQ_{10} against acute treatment with MPTP, which produced severe dopamine depletion in 5-month-old male mice. Transgenic mice with DJ-1 (Parkinson disease protein 7) deficiency (DJ-1/PARK7) with the hypersensitivity to MPTP showed a clear neuroprotection by a prophylactic use of Ubisol-Q_{10}, water-soluble nanomicellar formulation of CoQ_{10} (Muthukumaran *et al.* 2014b). Attia and Maklad (2018) indicated that CoQ_{10} supplement (200 mg/kg) caused a remarkable improvement in most of the behavioral tests and decreased protein carbonyl content in the brain in mouse PQ model, particularly when treatment of CoQ_{10} started prior rather than after PQ induction of PD. Ubisol-Q_{10} given in drinking solution (12 mg/kg/day) was effective in blocking the progression of neurodegeneration in PQ rat model when administered therapeutically (after PQ injection) (Muthukumaran *et al.* 2014a). However, Ubisol-Q_{10} must be given continuously and cannot be withdrawn in order to continue neuroprotection. The withdrawal led to further neurodegeneration. The authors suppose that Ubisol-Q_{10} halts neurodegeneration by supporting of remaining neurons (Muthukumaran *et al.* 2014a).

Furthermore, there are also cellular models, which develop pathology more quickly, do not require ethical approval and are less costly (Falkenburger *et al.* 2016). Treatment with water-soluble CoQ_{10} was succesful in human neuroblastoma (SH-SY5Y) cells paraquat model of PD (i.e. 10 μM paraquat in complete media for 48 hours at 37 °C), where it inhibited reactive oxygen species generation, reduced the number of apoptotic cells and DNA fragmentation (McCarthy *et al.* 2004). Another *in vitro* PD model of SH-SY5Y cells involved the addition of 6-hydroxydopamine (6-OHDA). 6-OHDA did not induce extensive oxidative damage of mitochondria but only a mild redox signal, which activated the machinery of mitochondrial fission and disrupted the mitochondrial morphology (Solesio *et al.* 2013). Treatment with mitochondria-targeted antioxidant MitoQ hand, IDB transfers electrons from complex II–succinate through its capacity to alter mitochondrial redox processes hand, IDB transfers electrons from complex II–succinate inhibited the migration of cytosolic dynamin-related protein-1 (Drp1) and pro-apoptotic protein Bax to the mitochondria and reduced the mitochondrial morphology alterations induced by 6-OHDA (Solesio *et al.* 2013). Xi *et al.* (2018) confirmed the protective effects of MitoQ on mitochondrial dynamics in 6-OHDA-induced *in vitro* (SN4741 cells derived from substantia nigra of mouse embryos) and *in vivo* models of PD (adult C57bl/6 male mice).

However, there are differences in the pathogenesis of the PD models and of human PD. PD models acts on complex I through a competitive inhibitory process for which CoQ_{10} supplementation is beneficial. The idea that supplementation of CoQ_{10} could retard the rate of PD progression of patients is rather old (Müller *et al.* 2003, Shults *et al.* 2002, Strijks *et al*. 1997, Yoritaka *et al.* 2015). Strijks *et al*. (1997) did not notice any beneficial effect in 10 patients treated with 200 mg of CoQ_{10} for 3 months. Shults *et al.* (2002) used three dosage of CoQ_{10} (300, 600 and 1200 mg/day) in 80 subjects with early PD for 16 months. The patients developed less disability, and the benefit was greatest in subjects receiving the highest dosage. Müller *et al.* (2003) indicated a moderate beneficial effect in PD patients (seven males and seven females) after oral application of 360 mg of CoQ_{10} lasting 4 weeks. Yoritaka *et al.* (2015) also indicated benefit for Japanese PD patients, who took 300 mg ubiquinol-10 capsules for 96 weeks. The reason can be that not all PD patients have low serum CoQ_{10} levels. Jiménez-Jiménez *et al*. (2000) found similar serum CoQ_{10} levels in 33 PD patients and 31 matched controls. However, earlier report showed decreased serum CoQ_{10} levels in PD patients (Matsubara *et al.* 1991).

Unfortunately, recent reviews and meta-analysis disclose that CoQ_{10} supplement plays only a limited role in the treatment of PD. It does not slow functional decline nor provides any symptomatic benefit for patients with PD (Negida *et al.* 2016, Oertel and Schulz 2016, Parkinson Study Group QE3 *et al*. 2014, Zhu *et al.* 2017).

Huntington's disease

Huntington's disease (HD), also known as Huntington's chorea or Saint Vitus' dance, is a rare autosomal dominant inherited neurodegenerative disease with the origin of symptoms at the age of 30-50 years. HD is characterized by progressive motor, behavioral and cognitive decline, resulting in death within 15 to 20 years after the diagnosis for which there is no effective therapy. The genetic defect of HD is caused by cytosine-adenine-

guanine (CAG) trinucleotide expansion in the huntingtin gene resulting in the production of an expanded polyglutamine in the mutant huntingtin protein. The cure is based largely on symptomatic treatment and lifestyle interventions with supportive management (Kumar *et al.* 2020, Yu and Bega 2019).

Mitochondria and energetic metabolism dysfunction as well as oxidative stress contribute to the neurodegenerative process (Koroshetz *et al.* 1997, Tobore 2019). However, antioxidant treatment with CoQ_{10} and vitamin E was not very successful in HD models. Combined administration (250 mg CoQ_{10} + 530 mg vitamin E/kg/day) could not prevent the decline of brain respiratory chain function in the HD model of Wistar rats injected with 3-nitropropionic acid (Kasparová *et al.* 2006). Combined supplementation did not also increase survival rates and pupal mortality of flies in the HD model of *Drosophila melanogaster* (Bahadorani and Hilliker 2008). It seems that antioxidants alone are not enough to delay or to stop the progress of HD. Two recent extensive reviews tried to answer the questions connected with the role of antioxidants and their therapeutic possibilities in HD (Bono-Yagüe *et al.* 2020, Essa *et al.* 2019).

Ranen *et al.* (1996) undertook a one-year, placebo-controlled, double-blind study with IDB. They did not find any significant differences between 91 patients receiving synthetic analogue of CoQ_{10} IDB (90 mg/day) or placebo group. The next placebo-controlled 30-month-trial tried to assess the impact of CoQ_{10} (300 mg twice daily) and a noncompetitive glutamatergic NMDA (N-methyl D-aspartate) receptor antagonist, remacemide hydrochloride (200 mg three times daily) but neither CoQ_{10} nor remacemide produced significant slowing in functional decline in early HD patients (Huntington study group 2001). On the other hand, several studies report beneficial effects of CoQ_{10} on behavior and pathology in mouse models of HD. The transgenic HD mice (R6/2) are widely used as a fast-progressing model in trials testing potential therapies. R6/2 mice with oral administration of CoQ_{10} or remacemide significantly increased survival and delayed the development of many HD symptoms. Combined treatment (CoQ_{10}+remacemide) was even more efficient (Ferrante *et al.* 2002). The authors suggest several potential explanations for the observed discrepancy: the dose of remacemide was 2.5-fold higher in mice, the pathophysiology of neurodegeneration in the transgenic mice may not be entirely reminiscent of that occurring in human patients and the disease stage in which the therapeutic trials were initiated was markedly different (Ferrante *et al.* 2002). Schilling *et al.* (2001) also found the amelioration of motor deficit but no prolonged survival of transgenic HD-N171-82Q mice after a combined treatment (CoQ_{10}+remacemide). Combined tetracycline antibiotic with antimicrobial and antiinflammatory properties minocycline and CoQ_{10} treatment provided an amelioration of behavior and neuropathological alterations (Stack *et al.* 2006). Moreover, this therapy improved motor performance to a greater degree than either minocycline or CoQ_{10} alone and significantly extended the survival of the R6/2 mice. In addition, combined minocycline and CoQ_{10} treatment attenuated gross brain atrophy, striatal neuron atrophy and specific protein huntingtin aggregation relative to the treatment with other drugs. However, Menalled *et al.* (2010) did not confirm the previously reported benefits. They found that neither CoQ_{10} nor minocycline caused significant improvements on measures of motor function or general health, e.g. open field, rotarod, grip strength, rearing-climbing, body weight and survival in the R6/2 mouse model. The authors discuss possible reasons of discrepancies, such as different founder lines of R2/6 mice, effect of nutrition and husbandry or number of experimental animals and behavior tests used. On the other hand, Hickey *et al.* (2012) used a slowly progressing HD model, the homozygote mutant CAG140 knock-in mouse, which expresses the full-length protein in the proper genomic context and may better reproduce human pathology. The mice display progressive motor, cognitive and emotional anomalies, transcriptional disturbances and late striatal degeneration. The authors report beneficial effects of 0.2 % CoQ_{10} in diet on motor behavior. Suprissingly, the lower (0.2 %) dose of CoQ_{10} was more effective than the higher (0.6 %) dose. The data emphasize that maximum benefit may be observed when treatment is begun at early stages of the disease, when neuropathological changes are minimal. It can explain the different results between Menalled *et al.* (2010) using the more rapid R6/2 mouse model and Hickey *et al.* (2012) who studied a slowly progressing CAG140 knock-in mouse model.

Another combined therapy (with creatine) produced additive neuroprotective effects, such as improving of motor performance and survival extension, in R6/2 transgenic mouse model of HD (Yang *et al.* 2009). Smith *et al.* (2006) performed a study administering high levels of CoQ_{10} to R6/2 transgenic

mice (from two different commercial sources). High doses of CoQ_{10} (1,000, 5,000, 10,000 or 20,000 mg/kg/day significantly extended survival and improved motor performance and grip strength, reduced weight loss and brain atrophy in R6/2 at 90 days.

Unfortunately, a recent multicenter randomized, double-blind study with 609 patients with early stage of HD (from the United States, Canada and Australia) obtaining 2,400 mg per day (or placebo) for 60 months showed no beneficial effect (McGarry *et al.* 2017). The trial was concluded early on the basis of an interim analysis and futility.

Alzheimer's disease

The most common, progressive, irreversible and fatal brain disease is Alzheimer's disease (AD), which disturbs cognition and memory functions. AD is strongly associated with increasing age with usual onset over 65 years old. Globaly, the greatest contributors to AD risk are smoking following by diabetes, mid-life hypertension, mid-life obesity, depression and physical inactivity (Barnes and Yaffe 2011). AD affects about 40 million individuals worldwide. AD's Association reports extensive analysis of information of AD, including incidence and prevalence, mortality rates, heath expenditures, cost of care and effect on caregivers and society in general in the Unites States (Alzheimer's Association 2013). Unfortunately, the cause of AD is not quite understood, the cure is not known, the prognosis remains poor, and the number of suffering people is increasing what impose an extreme burden to public healthcare systems worldwide. AD is characterized by the presence of pathological features in brain: amyloid-β peptide plaques and neurofibrillary tangles in pyramidal neurons. In addition, AD covers many neuropathologies and pathophysiological processes, such as neuroinflammation (Sochocka *et al.* 2017), oxidative stress (Atwood *et al.* 1999), vascular dysfunction (Di Marco *et al.* 2015), dendritic (Baloyannis 2009) and synaptic pathologies (Manyevitch *et al.* 2018). Damaged mitochondria also have an important role (Baloyannis 2006, Stanga *et al.* 2020, Wang *et al.* 2020). Moreover, Joshi *et al.* (2015) described Golgi apparatus fragmentation, which results in enhanced amyloid precursor protein and amyloid-β production.

Södeberg *et al.* (1992) reported increased levels of CoQ_{10} in *postmortem* brain samples. In observed brain regions of AD patients such as frontal cortex, precentral cortex, temporal cortex, frontal white matter, nucleus caudatus, hippocampus, pons, cerebellum and medulla oblongata, CoQ_{10} levels increased significantly compared to the controls, with the elevations varying between 30 and 100 %. The elevated levels of CoQ_{10} may reflect a change in oxidative stress (Södeberg *et al.* 1992). As concerns on plasma CoQ_{10}, De Bustos *et al.* (2000) compared serum CoQ_{10} level and CoQ_{10}/cholesterol ratio in 44 patients with AD, 17 patients with vascular dementia and 21 matched controls and the data were not significantly different. The values did not correlate with age, age at onset, duration of disease or score in cognitive tests. Other study confirmed no significant difference between 42 cognitively intact and 23 AD patients on plasma CoQ_{10} level (Giavarotti *et al.* 2013). However, Fišar *et al.* (2019) revealed an association between plasma CoQ_{10} concentration and the MMSE score in AD patients. The authors supposed that an even insignificant decrease in plasma CoQ_{10} concentration might play a role in the cellular dysfunction found in AD patients.

In the nineties, two smaller studies described improvements of memory, attention and behavior after IDB administration (Bergamasco *et al.* 1994, Senin *et al.* 1992). Gutzmann and Hadler (1998) conducted the two-year prospective, randomized, double-blind multicentre study with 450 patients with dementia of the AD type of mild to moderate degree. Their results suggested that IDB exerted its beneficial therapeutic effects on the course of the disease by slowing down its progression. However, Thal *et al.* (2003) in a one-year, multicenter, double-blind, placebo-controlled, randomized trial found that IDB failed to slow cognitive significant decline in 536 patients aged over 50 years with a diagnosis of probable AD and mild to moderate cognitive test (MMSE) scores. Patients were treated with three different doses of IDB 120, 240, or 360 mg three times daily. Galasko *et al.* (2012) discovered that antioxidants (400 mg of CoQ_{10} 3 times daily or 800 IU of vitamin E plus 500 mg of vitamin C plus 900 mg of α-lipoic acid daily) for 4 months did not influence cerebrospinal fluid biomarkers related to amyloid or tau pathology of patients with mild to moderate AD.

There are different mice models of AD disease. Yang *et al.* (2008) tested the effect of CoQ_{10} on β-amyloid in the 16-month-old transgenic mice overexpressing the Alzheimer presenilin 1-L235P mutation (leucine-to-proline mutation at codon 235). Mice, which were fed with CoQ_{10} (1,200 mg kg/day) for 60 days, effectively decreased amyloid-β overproduction

and depressed oxidative stress. Additionally, CoQ_{10} treatment improved markers of oxidative stress such as downregulation of superoxide dismutase and increased levels of malondialdehyde in transgenic mice relative to the wild-type mice. Another study found that CoQ_{10} treatment of TG19959 transgenic mouse model of AD decreased brain levels of protein carbonyls, a marker of oxidative stress, and provided protection against plaques and memory loss, as measured by the Morris water maze testing (Dumont *et al.* 2011). Transgenic mice with the P301S tau mutation, which causes frontotemporal dementia in man, were fed a control or 0.5 % CoQ_{10} diet (Elipenahl *et al.* 2012). The results show that CoQ_{10} significantly improved behavioral deficits and survival in transgenic mice with the P301S tau mutation. The authors also described a significant increase in mitochondrial complex I activity and protein levels and reduced oxidative stress with a reduction in lipid peroxidation. Muthukumaran *et al.* (2018) evaluated the neuroprotective effects of water-soluble formulation of CoQ_{10}, Ubisol-Q_{10} in drinking water (at a dose of 6 mg/kg/day) in one-month-old double transgenic male AD mice containing human/mouse chimeric amyloid β precursor and a mutant presenilin-1 gene. Ubisol-Q_{10} treatment reduced circulating amyloid peptide, improved long term memory, preserved working spatial memory and drastically inhibited amyloid plaque formation in 18-month-old transgenic mice compared to an untreated transgenic group. Ubisol-Q_{10} treatment also activated autophagy in AD fibroblasts (presenilin-1 mutated) as well as in the brains of transgenic AD mice (Vegh *et al.* 2019). The authors found increased expression of autophagy-related genes beclin-1 and JNK1 following Ubisol-Q_{10} treatment. However, withdrawal of Ubisol-Q_{10} treatment led to the return of the former phenotype in AD fibroblasts indicating that constant supplementation of Ubisol-Q_{10} is required.

The mitochondria-targeting antioxidant MitoQ significantly increased neurite outgrowth and synaptic connectivity in neuron cell culture from a mouse model of AD, amyloid-β precursor protein transgenic mice (Manczak *et al.* 2010). MitoQ treatment also prevented amyloid-β-induced oxidative stress and all death of mouse cortical neuron cell culture from another model of AD, triple transgenic mice expressing three mutant human genes: amyloid-β precursor protein, presenilin-1 and four-repeat tau (McManus *et al.* 2011). The study focused on prevention of AD development described the improvement of cognitive decline, oxidative stress, β-amyloid accumulation, astrogliosis, synaptic loss and caspase activation in young triple transgenic mice given MitoQ in the drinking watter at two months of age and continued for 5 months, i.e. the period during which the first AD-like pathologies become manifest (McManus *et al.* 2011). Young and Franklin (2019) focused on the therapy for AD. They evaluated the effects of MitoQ treatment on cognitive decline and neuropathologies in triple transgenic mice starting at 12 months after birth and continuing until 18 months of age, i.e. in the period during which all of the known AD-like pathologies are present and progressing. The authors found that MitoQ treatment of older AD mice was effective in improving memory retention compared to untreated mice. MitoQ-treated mice showed improved memory retention compared to untreated triple transgenic AD mice as well as reduced brain oxidative stress, synapse loss, astrogliosis, microglial cell proliferation, amyloid-β accumulation, caspase activation, and tau hyperphosphorylation. Additionally, MitoQ treatment inhibited synapse loss and significantly increased the abbreviated lifespan of the triple transgenic AD mice. These findings support the involvement of mitochondria-derived oxidative stress in the etiology of AD and suggest that MitoQ may lessen symptoms in AD patients.

Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is a devastating disease characterized by the death of motor neurons. The loss of motor neurons controlling voluntary muscles causes generalized progressive muscle weakness. Over time, patients lose the ability to walk, use their hands, speak, swallow, and breathe. Most ALS patients die within 3 to 5 years after diagnosis, usually as a result of respiratory failure. The ALS cause is mostly not known (about 10 % is familiar) and the effective therapy is still lacking. Mitochondrial alteration and oxidative stress are associated with ALS (Barber and Shaw 2010, Smith *et al.* 2019). Recently, Bond *et al.* (2018) and Wang *et al.* (2019) reported two systematic reviews on oxidative stress markers in ALS.

Molina *et al.* (2000) compared serum levels of CoQ_{10} and CoQ_{10}/cholesterol ratio in 30 patients with ALS and 42 matched controls using a high-performance liquid chromatography. The mean serum CoQ_{10} levels and the CoQ_{10}/cholesterol ratio did not differ significantly between the two studied groups. These values were not influenced by the clinical form (spinal vs. bulbar) of

ALS, and they did not correlate with age, age at onset, and duration of the disease. These results suggest that serum CoQ_{10} concentrations are unrelated to the risk for ALS. However, Sohmiya *et al.* (2005) observed a significant increase in oxidative form of CoQ_{10} and in the ratio of oxidized form of CoQ_{10} to total CoQ_{10}. Moreover, percentage of CoQ_{10} correlated significantly with the duration of illness suggesting systematic oxidative stress in the pathogenesis of the disease. Similarly, a significantly increased percentage of oxidized CoQ_{10} in total plasma CoQ_{10} in ALS patients was reported by Nagase *et al.* (2016). Significantly higher plasma levels of thiobarbituric acid-reactive species (TBARS), marker of lipid peroxidation damage, but without changes in concentrations of plasma antioxidants (α-tocopherol, β-carotene, ubiquinol-10 and glutathione) in ALS patients compared to healthy controls were described by Oteiza *et al.* (1997).

Matthews e*t al.* (1998) found that daily oral administration of 200 mg CoQ_{10}/kg attenuated striatal lesions produced by systemic administration of 3-nitropropionic acid and slightly but significantly increased life span in a transgenic mouse model of familial ALS. On the other hand, the treatment of mouse model of familiar ALS ($SOD1^{G93A}$) with oxidized (or reduced) CoQ_{10} had no effect on disease progression (Lucchetti *et al.* 2013). Experimental studies with targeted metabolic therapies supporting energy metabolism, which also contain CoQ_{10}, improved motor function, quality of life and survival time of ALS patients (Ari *et al.* 2014). A promising candidate for ALS treatment seems mitochondria-targeted antioxidant MitoQ, which has already been authorized for human medicine (Smith and Murphy 2010). Oral administration of MitoQ to SOD^{G93A} mice starting at the onset of the symptoms extended their survival and improved grip strength (Miquel *et al.* 2014). MitoQ in SOD^{G93A} mice also improved mitochondrial respiratory function in spinal cord and muscle, decreased nitrosative markers in central nervous system, decreased motor neuron loss and astrocyte reactivity in the spinal cord and maintained motor unit integrity.

In a clinical pilot trial, Ferrante *et al.* (2005) assessed the safety and tolerability of high doses of CoQ_{10} in ALS. They disclosed that doses as high as 3,000 mg CoQ_{10}/day are safe and well tolerated in 31 ALS patients for as long as 8 months. However, the serum CoQ_{10} level reached a plateau at a dose 2,400 mg/kg indicating that further studies need not exceed this high dose. Phase II trial of CoQ_{10} for ALS (dose selection with 35 participants per group) compared two doses: high (2,700 mg/day) and moderately high (1,800 mg/day) in 9-month-period (Levy *et al.* 2006, Kaufmann *et al.* 2009). Unfortunately, the authors did not find any significant differences between selected dose 2,700 mg CoQ_{10}/day and placebo subjects with 75 participants per group. Thus, the results did not provide sufficient evidence to justify a phase III trial for ALS treatment.

Friedreich's ataxia

Friedreich's ataxia (FA) is an autosomal recessive genetic and slowly progressive disease that causes difficulty in walking, a loss of sensation in the arms and legs and impaired speech. Moreover, life-threatening hypertrophic cardiomyopathy is the most severe manifestation. Reduced levels of the mitochondrial protein frataxin lead to cell-damaging oxidative stress (Bűrk 2017). CoQ_{10}, IDB and vitamin E were used as antioxidant treatment.

In an open-label study of 10 FA patients, antioxidant treatment (400 mg CoQ_{10} plus 2,100 IU vitamin E per day) did not show any consistent benefits in the neurological evaluation after 6-month treatment (Lodi *et al.* 2001). In all patient's serum CoQ_{10} level was increased and cardiac and skeletal muscle bioenergetics showed an improvement after 3-month-treatment (Lodi *et al.* 2001). The 4-year-follow-up study with 77 patients confirmed an improvement in cardiac and skeletal muscle mitochondrial energy synthesis but only 7 patients showed some neurological improvement (Hart *et al.* 2005). A high dose antioxidant therapy (600 mg CoQ_{10} plus 2,100 IU vitamin E per day) provided no additional benefit when compared to a very low-dose antioxidant therapy (30 mg CoQ_{10} plus 24 IU vitamin E per day) according to a two-year double-blind study with 50 FA patients (Cooper *et al.* 2008). Serum CoQ_{10} levels increased significantly in all patients. When compared cross-sectional data 49 % of all patients with CoQ_{10} brought some evidence for stabilizing effects on the progression of some neurological parameters monitored by International Cooperative Ataxia Ratings Scale (ICARS).

The early studies with antioxidant and synthetic analogue of CoQ_{10}, idebenone (IDB) used very low dose (5 mg/kg/day) and the numbers of participants were usually low (Artuch *et al.* 2002, Buyse *et al.* 2003, Mariotti *et al.* 2003, Rustin *et al.* 1999). The studies

showed various results in neurological aspects: from some improvement (Artuch *et al.* 2002, Di Prospero *et al.* 2007, Rustin *et al.* 1999) or no significant changes (Mariotti *et al.* 2003) till progressive worsening (Buyse *et al.* 2003). A retrospective analysis of 35 patients used IDB (5 mg/kg/day) for up to five years showed significantly deteriorated neurological parameters (Rinaldi *et al.* 2009). Brandsema *et al.* (2010) used intermediate dose of IDB (20 mg/kg/day) in 7 children's patients. More than one-year therapy did not statistically change ICARS and Pediatric Quality of Life Inventory scores. Markedly higher doses of IDB were used in randomized, double-blind, placebo-controlled study (IONIA) with 70 ambulatory pediatric patients who were treated with low doses: 450 or 900 mg of IDB per day depending on body weight (≤ or > 45 kg) or high doses: 1,350-2,250 mg of IDB per day depending on body weight (≤ or > 45 kg) (Lynch *et al.* 2010). The study did not show any significant neurological improvement during the 6-month period. Sixty-eight patients followed by a 12-month-study (IONIA-E) were treated only with a high dose of IDB: 1,350-2,250 mg/day depending on body weight (≤ or > 45 kg). The authors concluded that this dose may offer a therapeutic benefit to pediatric FA patients by stabilizing the overall neurological function and improving fine motor skills and speech (Meier *et al.* 2012). Comprehensive reviews on the use of CoQ_{10} and IDB in FA were prepared by Spindler *et al.* (2009) and Parkinson *et al.* (2013).

Multiple sclerosis

Multiple sclerosis (MS) is a chronic, autoimmune, inflammatory and demyelinating neurodegenerative disease of central nervous system with a broad spectrum of motor, sensory and neuropsychiatric symptoms but the etiology is still unknown. Although there are currently drugs that can alleviate the symptoms of MS, the cure is not known. Mitochondrial dysfunction and abnormalities play their role in MS pathology (Campbell *et al.* 2012, Witte *et al*. 2013). Oxidative stress also accompanies this disease (Acar *et al.* 2012, Choi *et al.* 2018, Haider *et al*. 2011, Tasset *et al.* 2012).

Gironi *et al.* (2014) estimated significantly lower blood CoQ_{10} levels in MS patients in comparison with healthy subjects. On the other hand, de Bustos *et al.* (2000) did not find any significant differences between serum CoQ_{10} (and the CoQ_{10}/cholesterol ratio) in a series of 31 patients with MS and 19 controls. Moreover, they did not find any correlation with age, age at onset or the duration of MS suggesting that the serum CoQ_{10} levels are an unrelated marker of risk or activity of MS. The possible explanation of the above difference can be that Gironi *et al.* (2014) had MS patients free of relapse or disease progression in the past 30 days, while de Bustos *et al.* (2000) studied patients during MS exacerbation. Therefore, the normal CoQ_{10} levels could be explained by an attempt of the organism to increase antioxidant mechanisms during an inflammatory phase of disease, which might thus compensate constitutive low CoQ_{10} levels Gironi *et al.* 2014).

CoQ_{10} supplementation (500 mg/day for 12 weeks) decreased levels of the marker of oxidative damage, malondialdehyde and increased the activity of antioxidant enzyme superoxide dismutase. Nevertheless, total antioxidant capacity was decreased, and glutathione peroxidase activity was not affected in 48 patients with relapsing-remitting MS in a double-blind, placebo-controlled randomized clinical trial (Sanoobar *et al.* 2013). The same CoQ_{10} supplementation (500 mg/day for 12 weeks) lowered levels of two pro-inflammatory markers: serum tumor necrosis factor-α and interleukin-6 but did not change levels of anti-inflammatory markers: tumor necrosis factor-β and interleukin-4 in 48 patients with relapsing-remitting MS (Sanoobar *et al.* 2015). Participants reported reduced fatigue and depression compared to the placebo group (Sanoobar *et al.* 2016). However, further clinical trials with long-term observation and more participants are needed to elucidate the benefit of CoQ_{10} particularly in the immune-related inflammation processes (Zahednasab *et al.* 2015). Moccia *et al.* (2019) evaluated the wide set of laboratory markers of oxidative stress and inflammation in 60 relapsing-remitting patients with MS treated with 44 μg interferon-ß1a and with 200 mg CoQ_{10}. After 3-month-period, CoQ_{10} supplementation improved the scavenging activity, reduced the oxidative damage and induced shift towards a more anti-inflammatory milieu in peripheral blood of patients.

CoQ_{10} is also mentioned in some papers dealing with the nutritional parameters and suitable diets for MS patients (Armon-Omer *et al.* 2019, Bagur *et al.* 2017, Evans *et al.* 2018, Marx *et al.* 2020, Zuliani and Baroni 2015).

The most widely used animal model of MS is mouse experimental autoimmune encephalomyelitis (EAE). Mao *et al.* (2013) found that EAE (C57BL/6) mice with MitoQ pretreatment and treatment (i.p. 100

nmol/mouse (~30 g) twice per week for several weeks) reduced axonal loss and neurological disabilities associated with EAE. Moreover, a mitochondria-targeted antioxidant MitoQ significantly suppressed demyelination and inflammation of EAE, including the inhibition of inflammatory cytokines and chemokines. The authors confirmed neuroprotective and antioxidant roles of MitoQ by a co-culture of cortical neurons and microglia designed to mimic the mechanism of MS and EAE *in vitro*. Similarly, CoQ_{10} administration (i.p. 10 mg/kg/three weeks) decreased significantly clinical symptoms and the level of the tumor necrosis factor α (TNF-α) versus interleukin 10 (IL-10) in EAE (C57BL/6) mice. Thus, CoQ_{10} was capable to suppress the inflammatory pathway of MS (Soleimani *et al.* 2014).

Another experimental model for studying demyelination-remyelination uses a copper chelator, cuprizol (CPZ), which inhibits copper ions and causes oxidative stress, oligodendrocyte apoptosis and demyelination. CoQ_{10} treatment of C57Bl/6 mice alleviated oxidative stress induced by CPZ and dramatically suppress infammatory biomarkers. (Khalilian *et al.* 2021).

Noise-induced hearing loss

Constant increased noice exposure is one of the most common causes of hearing loss. It is estimated that approximately 5 % of the world population suffers from noise-induced hearing loss (NIHL) but its management and treatment are only poorly understood. Recent systematic review includes eleven articles with 701 patients and determines the effectiveness of current pharmacologic agents for the prevention of NIHL (Gupta *et al.* 2021). Various regimens included administration several well-tolerated agents and known supplements such as α-lipoic acid, ambient oxygen, beta-carotene, carbogen, ebselen, Mg-aspartate, N-acetylcysteine, and vitamins C, E, and B_{12}. Unfortunately, there is only limited number of heterogenous studies and future prospective, double-blinded, randomized, placebo-controlled clinical trials with standardized reporting of audiometric data are necessary to evaluate the clinical efficacy of pharmacological prevention for NIHL (Gupta *et al.* 2021).

Oxidative stress is one of the current theories of NIHL. Fetoni *et al.* (2013) followed the relationship between cochlear oxidative damage and repeated noise exposure in rat model of adult male Wistar rats. NIHL caused hearing loss, damage in hair cells and spiral ganglion. In addition, NIHL changed dendritic morphology and decreased spine number of pyramidal neurons of auditory cortices. Systemic administration of a hydrophilic CoQ_{10} formulation (CoQ_{10} terclaclate – Q_{ter}, i.p. 10 mg CoQ_{10}/kg one hour before the acustic trauma) reduced oxidative-induced cochlear damage, hearing loss and cortical dendritic injury.

Hypertension

Hypertension belongs to cardiovascular diseases but the brain plays an essential role in arterial blood pressure regulation. Rostral ventrolateral medulla (RVLM) is a brainstem site that generates sympathetic vasomotor tone and is an important center of blood pressure control (Guynet 2006, Hirooka *et al.* 2010, Sved *et al.* 2003). Animal models of neurogenic hypertension such as spontaneously hypertensive rats (SHR) have elevated the levels of superoxide anion and hydrogen peroxide in RVLM (Kimura *et al.* 2005, Kishi *et al.* 2004, Konno *et al.* 2012, Tai *et al.* 2005). Chan *et al.* (2009) recognized reduced mitochondrial electron capacity in RVLM of SHR. Local microinjection of CoQ_{10} into RVLM of SHR restored a reduced mitochondrial electron transport chain capacity. Added CoQ_{10} lessened the rotenone inhibition of respiratory chain complex I or antimycin A inhibition of respiratory chain complex III. Local application of CoQ_{10} into RVLM of SHR promoted a dose-dependent decrease in mean arterial pressure and sympathetic vasomotor tone. On the other hand, there was only negligible effect of CoQ_{10} treatment on superoxide level in RVLM of prehypertensive SHR or normotensive Wistar Kyoto rats (Chan *et al.* 2009).

The paraventricular nucleus (PVN) in the hypothalamus also plays an important role in the development of hypertension. PVN is an important central site for the coordination and regulation of autonomic response involving several excitatory and inhibitory neurotransmitters and pro- and anti-inflammatory cytokines. Adult male Sprague-Dawley rats fed a high-salt (8 % NaCl) diet for 15 weeks developed hypertension with higher mean arterial pressure as compared to rats fed a normal salt (0.3 % NaCl) diet (Gao *et al.* 2016). High-salt diet also increased levels of noradrenaline, tyrosine hydroxylase, interleukin-1β, NADPH oxidase 2 (NOX2) and NADPH oxidase 4 (NOX4) and lowered levels of gamma-aminobutyric acid (GABA), interleukin-10 and Cu/Zn superoxide dismutase (SOD) in PVN. The

concomitant CoQ_{10} treatment (10 mg/kg/day via oral gavage in rats fed a high-salt diet) for 15 weeks attenuated salt-induced hypertension. Moreover, CoQ_{10} supplementation restored the balance between excitatory and inhibitory neurotransmitters and the balance between pro- and anti-inflammatory cytokines in PVN. Thus, Gao *et al.* (2016) concluded that CoQ_{10} exerts its protective effects on hypertension just via restoring the appropriated balance in PVN.

Rats fed a high-fructose diet are the well-established rodent model for the study of human metabolic syndrome (Wu *et al.* 2014). The feeding of a high-fructose diet for 8 weeks caused an increase in sympathetic vasomotor tone and neurogenic hypertension in adult male Sprague-Dawley rats. RVLM of rats fed a high-fructose diet had increased level of reactive oxygen species due to depression of mitochondrial electron transport chain capacity and neuronal NO synthase (nNOS) uncoupling *via* upregulation of its protein inhibitor. Intracisternal infusion of CoQ_{10} attenuated sympathoexcitation and hypertension and significantly ameliorated all molecular events in rats fed high-fructose diet.

These three examples of hypertension show the variety of CoQ_{10} actions – the restoration of mitochondrial respiratory chain (Chan *et al.* 2009) or the correction of the balance in neurotransmitters and cytokines (Gao *et al.* 2016).

Hypertension affects approximately one billion subjects worldwide and is a major risk factor associated with cardiovascular events including coronary heart disease and cerebrovascular accidents. Some reviews summarized that CoQ_{10} administration can lower blood pressure without significant side effects in patients (Ho *et al.* 2016, Rosenfeldt *et al.* 2007).

Conclusions

From the first pioneering clinical administration of CoQ_{10} to patients with heart failure in Japan in the 60s of the last century the number of CoQ_{10} applications keeps increasing. In the context of mitochondrial dysfunction and oxidative stress in the above-mentioned serious neurological diseases the most prominent and relevant functions are the energetic role and antioxidant capacity of CoQ_{10}. New promising formulations improve bioavailability and could make possible the more efficient administration. Unfortunately, the listed neurological diseases need a more causative treatment. CoQ_{10} administration can serve only as a corooborative substance. It is important to note that numerous clinical and experimental studies repeteadly provide the evidence that CoQ_{10} is highly safe and good tolerated with negligible side effects or drug interactions.

Conflict of Interest

There is no conflict of interest.

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