Review Article Open Access

Neurodegenerative and Fatiguing Illnesses, Infections and Mitochondrial Dysfunction: Use of Natural Supplements to Improve Mitochondrial Function.

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Submission date: November 08, 2013; Acceptance date: January 22, 2014; Publication date: January 25, 2014

ABSTRACT

Background: Many chronic diseases and illnesses are associated with one or more chronic infections, dysfunction of mitochondria and reduced production of ATP. This results in fatigue and other symptoms that occur in most if not all chronic conditions and diseases.

Methods: This is a review of the published literature on chronic infections in neurodegenerative diseases and fatiguing illnesses that are also typified by mitochondrial dysfunction. This contribution also reviews the use of natural supplements to enhance mitochondrial function and reduce the effects of chronic infections to improve overall function in various chronic illnesses.

Results: Mitochondrial function can be enhanced by the use of various natural supplements, notably Lipid Replacement Therapy (LRT) using glyerolphospholipids and other mitochondrial supplements. In various chronic illnesses that are characterized by the presence of chronic infections, such as intracellular bacteria (*Mycoplasma, Borrelia, Chlamydia* and other infections) and viruses, LRT has proven useful in multiple clinical trials. For example, in clinical studies on chronic fatigue syndrome, fibromyalgia syndrome and other chronic fatiguing illnesses where a large majority of patients have chronic infections, LRT significantly reduced fatigue by 35-43% in different clinical trials and increased mitochondrial function. In clinical trials on patients with multiple intracellular bacterial infections and intractable fatigue LRT plus other mitochondrial supplements significantly decreased fatigue and improved mood and cognition.

Conclusions: LRT formulations designed to improve mitochondrial function appear to be useful as non-toxic dietary supplements for reducing fatigue and restoring mitochondrial and other cellular membrane functions in patients with chronic illnesses and multiple chronic infections.

Key words: Neurodegenerative and fatiguing illnesses, infections and mitochondrial dysfunction, ATP, Lipid Replacement Therapy (LRT)

Background

Patients with chronic neurodegenerative, neurobehavioral and fatiguing illnesses commonly test positive for systemic and central nervous system (CNS) bacterial and viral infections [1-3]. In addition, other chronic illnesses where neurological manifestations are routinely found, such as autoimmune diseases and other chronic illnesses and disorders, also show evidence of systemic bacterial and viral infections that could be important in disease inception, progression and/or enhancing the types and severities of signs and symptoms [2, 3].

Evidence of bacterial infections, such as *Mycoplasma* species, *Chlamydia pneumoniae*, *Borrelia burgdorferi*, among others, and viruses, such as human herpesvirus (HHV), cytomegalovirus (CMV), human herpes viruses (HHV) and other viral infections, have revealed high rates of infection in the illnesses listed above that were not found in control populations [1-3]. Although the specific roles of chronic infections in various diseases and their pathogeneses have not been carefully determined, the data suggest that chronic bacterial and/or viral infections are common features of essentially all progressive chronic diseases [1-3].

Another common finding in chronic illness patients is mitochondrial dysfunction, characterized by loss of efficiency in the electron transport chain, reductions in mitochondrial inner membrane trans-membrane potential and reductions in the synthesis of high-energy molecules such as ATP [4-6]. This is also a characteristic of aging, and it essentially occurs in all chronic diseases, including cancer [5-7].

This review will concentrate on commonly acquired mechanisms that affect mitochondrial function. To treat functional loss associated wtih chronic infections mitochondrial replacement strategies with natural supplements and combinations of natural supplements have been used, including vitamins, minerals, enzyme cofactors, antioxidants, metabolites, transporters, membrane-type phospholipids and other natural supplements in order to improve mitochondrial function.

Introduction

Chronic infections appear to be a common feature of various diseases, including neurodegenerative, psychiatric, neurobehavioral diseases and other conditions [1-3, 8]. Chronic infections are also associated with autoimmune diseases [9, 10] and fatiguing illnesses [1, 3, 11]. This will be discussed in various sections of this review. In addition, many chronic illnesses are directly caused by chronic infections, such as Lyme disease, brucellosis, babesiosis, and other infection-based chronic diseases [2, 12-14].

Chronic infections collectively result in induction of excess Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS) that damage cellular structures, especially mitochondrial membranes [15-17]. Mitochondria are especially sensitive to excess levels of ROS/RNS, and in chronic illnesses there is extensive damage to mitochondria in the form of membrane oxidation, damage to mitochondrial DNA (mtDNA) and loss of mitochondrial enzymatic function and inner mitochondrial membrane potential [6-8, 18-20]. In this review we will discuss the use of

comprehensive approaches to restore mitochondrial function damaged by infections and other causes.

Patients with chronic illnesses (often caused by or exacerbated by chronic infections) are particularly difficult to treat using single modality approaches, and this is particularly true for patients who have multiple chronic infections [21, 22]. The multi-focal nature of chronic diseases and the fact that often treatments are given to suppress adverse signs and symptoms, rather than treat causes of the disease or its progression, have resulted in incomplete or ineffective treatments. On the other hand, even if the causes of chronic diseases are known, by the time therapeutic interventions are undertaken, it may be entirely too late to use approaches that might work on the disease at an early stage or if chronic infections were not also present. At the stage(s) of disease when patients usually seek medical care for their conditions, they usually have multiple problems, including chronic infections, and each of these problems usually requires complex therapeutic approaches. Their multiple chronic infections also cause additional cellular damage [1, 2, 8].

Multiple alternations in mitochondrial membranes, proteins and mtDNA are thought to be the cause for mitochondrial dysfunction, and this damage can also accumulate over time [6, 23]. By the time patients seek care, they usually have multiple defects in their mitochondria, and thus there are no simple approaches that are effective in promoting functional recovery of their mitochondria. With this in mind, we have begun this review by discussing the evidence for chronic infections and mitochondrial dysfunction in selected chronic illnesses and diseases. Then we will discuss the role that various supplements play in restoring mitochondrial function, even in patients with multiple chronic infections that continue to degrade mitochondrial components. Finally we will discuss the role of combination supplements for restoring mitochondrial function in patients with chronic illnesses and multiple chronic infections.

Neurodegenerative Diseases

Neurodegenerative diseases, or chronic degenerative diseases of the central nervous system (CNS) that cause dementia, are mainly diseases of the elderly [1, 2]. On the other hand, neurobehavioral diseases are found mainly in young patients and include autism spectrum disorders (ASD), such as autism, attention deficit disorder, Asperger's syndrome and other disorders [24]. For the most part, the causes of these neurological diseases remain largely unknown but it is thought that multiple factors are involved in each disease [1, 2].

Neurodegenerative diseases are characterized by molecular and genetic changes in nerve cells that result in nerve cell dysfunction, degeneration and ultimately cell death, resulting in neurological signs and symptoms and eventually dementia [1, 2]. In contrast, neurobehavioral diseases are related to fetal brain and early post-partum development but are less well characterized at the cellular level. Both of these disease types involve genetic and environmental factors [24, 25], and they also have multiple chronic infections [1-3, 26, 27]. Even less well characterized at the cellular and genetic level are the psychiatric disorders, such as schizophrenia, paranoia, bipolar disorders, depression and obsessive-compulsive disorders, but these diseases are also associated with the presence of chronic infections [3].

Genetic alternations have been found in neurodegenerative and neurobehavioral diseases, but the genetic changes as well as changes in gene expression that have been found are complex

and usually not directly related to simple gene alterations, such as single mutations and deletions, that lead to single protein molecule alterations [24, 25, 28]. Importantly, mutations that affect mitochondrial function are known to be associated with neurodegenerative and neurobehavioral diseases [29, 30]. These include mutations in mtDNA as well as nuclear DNA [29]. In addition to chronic infections and genetic changes, environmental toxins, heavy metals, nutritional deficiencies, autoimmune immunological responses, vascular diseases, head trauma (and accumulation of fluid in the brain), changes in neurotransmitter concentrations, among other elements, are thought to be collectively involved in the pathogenesis of various neurodegenerative and neurobehavioral diseases [1, 2, 24-31]. These important topics will not be discussed in detail in this review.

Chronic Infections are important factors in neurodegenerative and neurobehavioral diseases, and infectious agents may enter the brain within infected migratory macrophages. Alternatively, they can also gain access by direct penetration of the blood-brain-barrier or entry by intraneuronal transfer from peripheral nerves [32]. Cell wall-deficient bacteria, such as species of *Mycoplasma, Chlamydia* (*Chlamydophila*), *Borrelia, Brucella*, among others and various viruses are candidate brain infectious agents, because they are capable of CNS penetration and have been found routinely in neurodegenerative and neurobehavioral diseases [1-3, 26, 27, 32, 33]. Such infections are usually systemic and can affect immune systems and essentially any organ system, resulting in a variety of systemic signs and symptoms that are not limited to the CNS [10, 11, 26, 27, 32, 33].

Amyotrophic lateral sclerosis (ALS)

ALS is an adult-onset, progressive neurodegenerative disease of unknown etiology that affects both central and peripheral motor neurons where patients show gradual progressive weakness and paralysis of muscles due to destruction of upper motor neurons in the motor cortex and lower motor neurons in the brain stem and spinal cord [34, 35]. Eventually this results in death, usually by respiratory failure [35].

Chronic infections in ALS, such as the finding of enterovirus sequences in a majority of ALS spinal cord samples by polymerase chain reaction (PCR) [36], have attracted widespread attention. However, others have failed to detect enterovirus sequences in ALS spinal cord samples [37]. Using PCR methods systemic mycoplasmal infections have been found in a high percentage (83%) of ALS patients [38]. For example, all of the tested Gulf War veterans diagnosed with ALS from three nations had systemic mycoplasmal infections [38]. In addition, a majority of ALS patients in Lyme endemic areas show immunological evidence of Borrelia infections [39], and some patients diagnosed with ALS were subsequently found to have neuroborreliosis infections [40]. Although high rates of infection may occur in certain regions, the overall rate of Borrelia infections in ALS is low (10% or less) in North America [41]. MacDonald [42], however, observed a high incidence of spirochetal forms in the brain tissues of ALS patients and in patients with other neurodegenerative diseases, suggesting that the presence of chronic bacterial infections in the CNS of neurodegenerative diseases patients is much more common than previously assumed.

ALS patients also show evidence of other infections. These include: human herpes virus-6 (HHV-6), *Chlamydia pneumoniae*, cyanobacteria and other infections [43-45]. Chronic

infections plus other defects (accumulation of glutamate causing excitotoxicity, deficiency of nerve growth factor, autoimmune reactions against motor neurons and dysfunction of mitochondrial superoxide dismutase) have been proposed to be important in ALS pathogenesis [review: 2].

Mitochondrial dysfunction is a common feature of ALS and animal models of ALS [46, 47]. Evidence from patients with sporadic and familial ALS and from ALS models based on the over-expression of mutant SOD1 found in a small subset of patients, clearly point to mitochondrial damage as a relevant facet of this neurodegenerative condition [46]. In addition to mutations in superoxide dismutase genes, some ALS patients present with mutations in mitochondrial transport genes and misfolding in inclusion proteins, ubiquilin-2 and other mitochondrial associated proteins [review: 47]. Dysfunction in several other cellular mechanisms, including mitophagy, oxidative stress, lipid peroxidation and cholesterol esterification, protein and neurofilament aggregation, impaired axonal transport, among other changes in ALS patients have been reviewed recently [47, 48].

Multiple Sclerosis (MS)

The most common demyelinating neurological disease is MS [49]. MS can occur in all age groups as a cyclic (relapsing-remitting) or a progressive disease that continues progressing without remitting [49]. Inflammation and the presence of autoimmune antibodies against myelin and other nerve cell antigens are thought to cause myelin sheath breakdown, resulting in decrease or loss of electrical impulses along nerve fibers [49, 50]. In the MS patients with progressive neurological symptoms damage occurs additionally by the deposition of plaques on nerve cells to the point where nerve cell death occurs. Importantly, breakdown of the blood-brain barrier in the CNS of MS patients is associated with local inflammation caused by activated glial cells [49, 50]. The combination of demyelinization, plaque damage and blood-brain barrier disruption causes multiple, variable symptoms, but they usually include impaired vision, alterations in motor, sensory and coordination nerve systems along with cognitive dysfunction [50].

MS is a disease in which environmental, genetic and epigenetic factors determine the risk of developing MS, its progression and responsiveness to treatment [51, 52]. Just as in ALS, there are multiple genetic components in MS [51, 53]. Although it has been established that there is a genetic basis to MS susceptibility, epidemiological and twin studies suggest that MS is basically an acquired disease with some genetic and environmental components [54].

The molecular mechanisms through which environmental signals are translated into changes in gene expression include: DNA methylation, post-translational modification of nucleosomal histones, and non-coding RNAs. These mechanisms are regulated by families of specialized enzymes that are tissue-selective and cell-type specific [54].

Chronic infections have been linked to the pathophysiology of MS [55, 56]. For example, MS patients show immunological and cytokine elevations consistent with chronic infections [57, 58]. An infectious basis for MS has been under examination for some time, and patients have been tested for various viral and bacterial infections [1, 3, 53, 55, 56].

One of the most consistent findings in MS patients has been the presence of *C. pneumoniae* antibodies and DNA in their cerebrospinal fluid [59-61]. By examining relapsing-remitting and

progressive MS patients for the presence of *C. pneumoniae* in cerebrospinal fluid by culture, PCR and immunoglobulin reactivity Sriram et al. [60] were able to identify *C. pneumoniae* in 64% of MS cerebrospinal fluid versus 11% of patients with other neurological diseases. They also found high rates of PCR-positive MOMP gene (97%) in MS- patients (versus 18% in other neurological diseases), and this correlated with a high rate of patients being serology-positive (86%) for *Chlamydia* antigens by ELISA and Western blot analysis [60]. MS patients examined for oligoclonal antibodies against *C. pneumoniae* revealed that 82% of MS patients were positive compared to none of the control non-MS neurological patients [61]. Similarly, *C. pneumoniae* RNA and DNA transcripts were found in mononuclear cells and cerebrospinal fluids of 64.2% of MS patients but in only 3 controls [62].

The brain tissues of MS and non-MS neurological patients have also been examined for *C. pneumoniae* antigens [63]. Using immunohistochemistry to find *C. pneumoniae* antigens in formalin-fixed brain tissue Sriram et al. [63] found that in a subset of MS patients (35%) Chlamydial antigens were localized to ependymal surfaces and pariventricular regions. Positive reactions were not found in brain tissue samples from other neurological diseases. PCR amplification of *C. pneumoniae* genes was accomplished in 63% of brain tissue samples from MS patients but none in frozen brain tissues from other neurological diseases. In addition, using immuno-electron microscopy the sediment from cerebrospinal fluid was examined for Chlamydial antigens [63]. Sriram et al. [63] found that the electron dense bodies resembling bacterial structures that were positive by immuno-electron microscopy correlated with tissue PCR-positive MS cases (91% positive using both methods).

Using different nested PCR methods to examine additional *C. pneumoniae* gene sequences in the cerebrospinal fluid of 72 MS patients Contini et al. [64] were able to match these results to MS-associated lesions seen by MRI. Grimaldi et al. also used MRI to link the presence of *C. pneumoniae* infection with abnormal MRI results and found linkage in 21% in MS patients [65]. The MS patients with *C. pneumoniae* infections were also the MS patients with more progressive disease. Indeed, higher rates of *C. pneumoniae* transcription were found in the cerebrospinal fluid of 84 patients with the more progressive form of MS [66]. These studies strongly support the presence of *C. pneumoniae* in the brains of MS patients with progressive disease [67, 68].

Not all researchers have found *C. pneumoniae* or other bacteria in the brains of MS patients [69, 70]. For example, Hammerschlag et al. used nested PCR and culture to examine frozen brain samples from MS patients but could not find any evidence for *C. pneumoniae* gene sequences [71]. Thus the evidence linking *C. pneumoniae* infection with MS is not universally accepted, and other genetic changes may be necessary to complete the link between such infections and the etiology of MS [72].

Multiple infections in MS patients may complicate the evidence linking MS with specific chronic infections. Thus other infections similar to *C. pneumoniae* could be involved rather than just one specific infection [1]. In addition to *C. pneumoniae*, MS patients could also have *Mycoplasma* species, *B. burgdorferi* and other bacterial infections as well as viral infections [73]. When multiple infections are considered, it is likely that >90% of MS patients have obligate intracellular bacterial infections.

Various viruses have also been found in MS patients. For example, HHV-6 has been found at higher frequencies in MS patients, but this virus has also been found at lower incidence in

control samples [74]. PCR was used to examine postmortem brain tissue and controls for the presence of various neurotrophic viruses [74]. These studies revealed that 57% of MS cases and 43% of non-MS neurological disease controls contain sequences for HHV-6, whereas 37%, 28%, and 43%, respectively, contained sequences for herpes simplex virus (HSV)-1 and –2 and varicella zoster virus. Although impressive, the data did not achieve statistical significance. They also found that 32% of the MS active plaques and 17% of the inactive plaque areas were positive for HHV-6 [74].

Using sequence difference analysis Challoner et al. searched for pathogens in MS brain specimens and found that >70% of MS patients were positive for infection-associated sequences [76]. They also used immunocytochemistry and found positive staining around MS plaques more frequently than around surrounding white matter. Additionally, HHV-6 DNA was found in peripheral leukocytes in the systemic circulation of MS patients [77] but not in every study [78].

Examination of the literature strongly suggests an infectious process in MS [1, 55, 56, 79, 80]. In most studies the more progressive forms of MS rather than the relapsing-remitting forms of MS were associated with chronic infections. Thus chronic infections may play a role in progression of MS. If infections like *C. pneumoniae* and *Mycoplasma* species are important in MS, then antibiotics effective against these infections should improve clinical status [1]. This has, in fact, been seen in most but not in all MS patients [81]. As in other neurodegenerative diseases, multiple factors appear to be involved in the pathogenesis of MS [1, 49, 55, 56, 82].

One of the factors in MS appears to be mitochondrial dysfunction due to oxidative injury [83, 84]. Broadwater et al. have identified several MS-related damaged mitochondrial proteins that are involved in respiration, including cytochrome c oxidase subunit 5b, an isozyme of creatine kinase, and hemoglobin □eta chain [85]. One of the lesions in MS mitochondria appears to be damage to the permeability transition pore (PTP) by excess reactive oxygen species (ROS) [86]. This critical structure is central to mitochondrial dysfunction by allowing ion dysregulation within neural cells that drives neurodegeneration by allowing the PTP to change the ion gradients inside mitochondria, lowering inner membrane trans-membrane potential (thus reducing oxidative phosphorylation [87]), promoting matrix expansion leading to release of cytochrome c and initiating cell death programs [86]. In addition, the energy and calcium balance in neurons plays an important role in maintaining a healthy myelin sheath, and a hallmark of MS is axon demyelation due to mitochondrial dysfunction [83], which drives an inflammatory response characteristic of MS progression [88].

Alzheimer's disease (AD)

AD is characterized by distinct pathological changes in brain cells and tissues [1, 2]. Among the most notable are the appearance of plaques and tangles of neurofibrils in brain nerve cells that affect synapses and nerve-nerve cell communication. These alterations involve the deposition of altered amyloid proteins [89, 90]. Although the origins of AD are not known for certain, the formation of the amyloid plaques and neurofiber tangles found in AD may be due to genetic defects and resulting changes in the structure of beta amyloid proteins, which may be caused by chemicals or other toxic events, inflammatory responses, excess oxidative stress and increases in ROS, loss of nerve trophic factors and reductions in nerve cell transmission [89-92].

Infections are potentially important in the AD disease process [93, 94]. One pathogen that has attracted considerable attention because of its neurotropism is *C. pneumoniae* [95, 96]. This intracellular bacterium has been found at high incidence in the brains of AD patients by PCR and immunohistochemistry [96]. *C. pneumoniae* has also been found localized in nerve cells in close proximity to neurofibrillary tangles, a characteristic of AD [96, 97].

C. pneumoniae can invade endothelial cells and promote the transmigration of monocytes through human brain endothelial cells into the brain parenchyma [98]. *C. pneumoniae* has been found in the brains of most AD patients [95], and it has been cultured from the brain tissue of AD patients [99]. Immunohistological detection of *C. pneumoniae* was observed inside and outside cells in the frontal and temporal cortices of AD brains [100]. Indeed, in experiments with mice injection of *C. pneumoniae* stimulated brain beta amyloid plaque formation [101]. The data are compelling, but some investigators have not been able to duplicate the findings on infections in AD [102].

In addition to *C. pneumoniae* investigators have found other infections in AD patients, such as *B. burgdorferi* [103, 104]. Using serology, culture, Western blot and immunofluorenscence methods this infection has been examined in AD patients (with or without a diagnosis of Lyme disease) and found to be present [104, 105]. The presence of intracellular infections like *B. burgdorferi* in AD patients has been proposed to be a primary event in the formation of AD beta amyloid plaques, which are thought to occur by the formation of "congophilic cores" that attract beta amyloid materials [106]. In fact, exposure of glial and neuronal cells in vitro to *Borrelia burgdorferi* spirochetes and to the inflammatory bacterial lipopolysaccharide LPS caused morphological changes analogous to those found in deposits in AD brains [107]. Also detected were increases in beta amyloid precursor protein and hyperphosphorylated tau protein characteristic of AD [107]. Several reports indicate that AD nerve cells are often positive for *B. burgdorferi*, indicating that this intracellular bacteria could be important in the pathogenesis of AD [103-106, 108]. However, there are reports that could not find evidence for the presence of *Borrelia* in AD brain tissue [109].

Miklossy has reviewed the data indicating that chronic infections, including *B. burgdorferi*, are commonly found in AD patients and has concluded that intracellular bacteria contain amyloidogenic proteins that can induce amyloid beta deposition and tau phosphorylation [110, 111]. In addition, specific bacterial ligands and bacterial and viral DNA and RNA increase the expression of proinflammatory molecules that activate the innate and adaptive immune systems. Evasion of brain pathogens from destruction by the host immune system can result in persistent infection, chronic inflammation, neuronal destruction and beta amyloid deposition [111].

The hypothesis that intracellular microorganisms or their protein products can induce beta amyloid protein and then provide "nucleation sites" for the attraction of beta amyloid materials is attractive [111], but other factors, including the induction of reactive oxygen species, lipid peroxidation and the breakdown of the lysosomal membranes releasing lysosomal hydrolases, are also thought to be important in beta amyloid deposition [108]. An infectious basis in AD pathogenesis is attractive; however, although some negative reports imply that infections like *B. burgdorferi* are not essential in AD pathogenesis [109]. On the other hand, other intracellular bacterial infections (*Mycoplasma, Chlamyda, Helicobacter* etc.) have been found in AD patients and could be present in those patients who are negative for Borrelia infections [111-113]. It has

been proposed that chronic infections may be important cofactors in AD and contribute to the pathogenic process [113].

Viral infections may also play a role in AD pathogenesis. Herpes virus infections, especially HSV-1, have been found in AD patients [114, 115]. Previously it was determined that HSV-1 but not a related neurotrophic virus (varicella zoster virus) was present more often in AD brains, and this could be linked to patients who have the AD risk factor ApoE e4 allele [116, 117]. Similar to bacterial proteins, HSV-1 proteins may also be involved in the abnormal aggregation of beta amyloid fragments within the AD brain, but in this case by reducing the amount of full-length beta amyloid precursor protein and increasing the amounts of their fragments [118]. HSV-1 infection of glial and neuronal cells resulted in a dramatic increase in the intracellular levels of beta amyloid forms, whereas the levels of native beta amyloid precursor protein decreased [119]. This has been found in mice infected with HSV-1, indicating that HSV-1 is probably involved directly in the development of senile-associated plaques. Other herpes viruses, such as HHV-6, have also been found in AD patients, but it is thought that this virus is not directly involved in AD pathogenesis. Another virus that has been implicated in AD is cytomegalovirus [120]. A high proportion of brains from vascular dementia patients show evidence of both HSV-1 and cytomegalovirus [120].

Mitochondrial dysfunction may be an early event in the pathogenesis of AD [121-123]. AD patients show impairments in mitochondrial function that start early in process of neurodegeneration [121, 123]. Mutations in the AbetaPP and tau genes induce oxidative stress and mitochondrial dysfunction leading eventually to apoptotic cell death [124]. Indeed, transgenic mouse models of AD point to impairments in oxidative phosphorylation as an important aspect of AD pathogenesis [125]. The oxidative stress is thought to cause protein alterations that have synergistic effects on mitochondria, leading to synaptic dysfunction and apoptotic cell death [124].

Parkinson's Disease (PD)

PD is characterized by akinesia, muscular rigidity and tremor. In addition, autonomic dysfunction, olfactory disturbances, depression, sensory and sleep disturbances and frequently dementia characterize this disease [126]. The pathology indicates a progressive loss of the dopamine neurons of the substantia nigra together with the presence of Lewy bodies and □lpha-synuclein. Extensive brain degeneration also occurs in PD [127]. Inclusion bodies and protein aggregations or defects in their degradation characteristically are characteristic of PD, but their role in PD pathogenesis is unclear [127, 128]. Available evidence suggests a relationship between PD and specific genetic changes, such as changes in the genes in mitochondria, those affecting protein degradation, organelle trafficking and vesicular fusion, and in proteins involved in oxidative stress or antioxidant function [129. 130]. Inflammation has also been associated with PD [131].

PD has been proposed to be due to neurotoxic events in genetically susceptible individuals that are especially sensitive to neuro-oxidative damage [132]. Multiple environmental factors and genetic background are also statistically related risk factors for PD [133]. The mitochondria in neuromelanin-containing dopaminergic neurons of the substantia nigra are the targets for oxidative damage [128, 133, 134], and early life exposures are also important [135]. For

example, early life exposure to brain injury, chemicals and/or infections may initiate a cyclic inflammatory process involving oxidative damage, excitotoxicity, mitochondrial dysfunction and altered proteolysis that later in life results in neuron death in the substantia nigra [136, 137].

Chronic infections have been proposed as important in PD pathogenesis [136, 137]. In fact, regression analysis of a case-control study on infections in PD patients clearly showed that infectious processes are an important risk factor in PD [138]. One infection found in PD that has aroused considerable interest is the presence of chronic gastrointestinal *Helicobacter pylori* infections [139]. Treatment of this infection in PD patients offered relief from late stage cachexia [140]. *Helicobacter pylori*-infected PD patients also showed reduced L-dopa absorption and increased clinical disability [141], and in antimicrobial-treated PD patients there was increased L-dopa absorption and decreased clinical disability [142]. Although *H. pylori* may not be directly involved in the pathogenesis of PD, its systemic presence has been proposed to affect the progression and treatment of PD [141].

PD patients' chronic infections have been linked to autoimmunity and inflammation [143-145], and the role of neuro-inflammatory and oxidative processes in nigral degeneration has gained increasing attention [145, 146]. Moreover, experimental models of PD have been developed using viral or bacterial infections to initiate the pathogenic process [147, 148]. In examining PD patients various infections have been found, especially bacterial and viral infections [144, 149]. For example, spirochetes have also been found in the brain Lewy bodies of Lyme-associated PD patients [150]. Other infections, such as viral encephalitis [151], cornavirus [152], *Mycoplasma pneumoniae* [153], AIDS-associated infections of the basal ganglia [154], HIV [155], among other infections, have been found in PD patients [144, 149, 155]. Additional research will be necessary to establish whether a causal link exists between PD and chronic infections [143, 155, 156].

A common link between oxidative stress, mitochondrial dysfunction and PD exists [157, 158]. Although the underlying mechanisms for selective dopaminergic nerve degeneration in PD are not completely known, the increase in ROS in Parkinson's substantia nigra neurons results in increased DNA mutation, especially in mtDNA, reduced efficiency of the electron transport chain, and changes in protein aggregation and lipid oxidation that contribute to mitochondrial destruction (mitophagy) and neurodegeneration [132, 145, 156-158]. Mutations in genes that protect neural cells from oxidative damage-mediated mitochondrial dysfunction, such as tensin (PTEN) homologue-induced kinase-1 (PINK1), are known to be associated with recessively inherited PD, and this also points to mitochondrial damage as an underlying defect in PD [159]. PINK1 is involved in mitochondrial quality control, and under steady state conditions PINK1 is rapidly and constitutively degraded in a mitochondrial membrane potential-dependent manner [160]. Loss of mitochondrial inner membrane potential stabilizes PINK1 mitochondrial accumulation and stimulates the initiation of autophagic degradation and removal of damaged mitochondria (mitophagy), but mutations in PINK1 inhibit this process [161]. This implicates loss of mitochondrial integrity and mitophagy in the pathogenesis of PD.

Neurobehavioral Diseases

Autism spectrum disorders (ASD)

ASD includes autism, Asperger's syndrome, among other disorders. These diseases affect primarily young patients who generally suffer from an inability to properly communicate, form relationships with others and respond appropriately to their environment. ASD patients do not all share the same signs and symptoms but tend to have in common certain social, communication, motor and sensory problems (non-compliance, hyperactivity, sensory defensiveness, self-injury, among others) that affect their behavior. They can display repetitive actions and develop troublesome fixations with specific objects, and they are often painfully sensitive to certain sounds, tastes and smells [162, 163].

Multiple factors appear to be involved in ASD, including genetic factors, environmental exposures, such as heavy metals and chemicals and biological exposures, which are probably different in each patient [27, 28, 164-169]. ASD patients appear to have similarities in genetic defects and environmental exposures that have been proposed to play interactive roles that are probably important in patient morbidity or in illness progression [170, 171].

Chronic infections appear to be an important element in the development of ASD [2, 26, 27, 168, 169]. In ASD patients more than 50 different bacterial, viral and fungal infections have been documented [27]. A few of these occur at high incident rates and may be more important than others in causing ASD symptoms [2, 169]. ASD patients also present with a number of nonspecific chronic signs and symptoms that suggest infections, such as fatigue, headaches, gastrointestinal and vision problems as well as intermittent low-grade fevers and other signs and symptoms [169, 172]. Increased titers to various viruses as well as bacterial and fungal infections have been commonly seen in ASD patients [27, 169, 172-174].

Infections along with environmental exposures to chemicals and heavy metals is controversial but in some cases may be important in the development of ASD in genetically susceptible children [27, 28,166-174]. The relationship between ASD and heavy metals is controveral but could be linked to the multiple vaccines given during pre-school years [166, 167]. ASD often developes only after multiple childhood immunizations, and the sharp increase in Autism may be linked to vaccines after they came into widespread use [167]. Many of these vaccines contain mercury and other toxic preservatives, and some may also contain contaminating bacteria, as found in 6% of veterinary vaccines [175]. ASD is also related to environmental infections, such as Lyme *Borrelia* and associated co-infections [21, 27, 169, 174].

An interesting study on the transmission of infections and subsequent ASD has come from the families of veterans of the Gulf War [176, 177]. After veterans with Gulf War Illness returned to the home, their children subsequently became symptomatic, and these children were often diagnosed with ASD [178]. Symptomatic children with ASD were infected with the same *Mycoplasma* species, *M. fermentans*, that was found in the veterans and their symptomatic family members, and this was not seen in aged-matched control subjects or in military families without GWI. In these families some non-symptomatic family members did have mycoplasmal infections (~10%), but this was not significantly different from the incidence of mycoplasmal infections in healthy control subjects [177, 178].

Non-military families were also examined for systemic mycoplasmal infections [26]. In the ASD cases a majority were positive for mycoplasmal infections. In contrast to the children from military families who for the most part had only *M. fermentans*, the civilian children tested positive for a variety of *Mycoplasma* species [26]. For example, a large subset (>58%) of ASD

patients showed evidence of *Mycoplasma* infections compared to age-matched control subjects (Odds Ratio=13.8, p<0.001). ASD patients were also examined for *C. pneumoniae* (8.3% positive, Odds Ratio=5.6, p<0.01) and HHV-6 (29.2% positive, Odds Ratio=4.5, p<0.01). The results indicated that a large subset of ASD patients have bacterial and/or viral infections (Odds Ratio=16.5, p<0.001) [26].

In addition to *Mycoplasma* infections, many ASD patients have *B. burgdorferi* infections [179]. Various studies revealed that 22-30% of ASD patients have *Borrelia* infections [169]. The incidence of *Borrelia* infections in ASD patients may be related to Lyme disease distribution, and other Lyme-associated infections, such as *Bartonella, Babesia, Ehrlichia*, may also be present in ASD patients [169].

Mitochondrial dysfunction is a common finding in ASD [180, 181]. Many mitochondrial biomarkers were significantly different between ASD patients and controls, and some markers correlated with ASD signs and symptoms severity [181]. Because of the similarities in symptoms, mitochondrial dysfunction in ASD patients may be related to non-ASD mitochondrial disease [181]. In addition, there was also an association between ASD and immune dysregulation and inflammation, oxidative stress, and toxicant exposures [182]. Palmieri and Persico have proposed that mitochondrial dysfunction in ASD is a down-stream affect, since it cannot be directly linked to many genetic or genomic defects found in ASD patients. Thus mitochondrial dysfunction in ASD may be due to the consequences of dysreactive immunity or altered calcium signaling [183].

Fatiguing Illnesses

Fatigue is usually understood as a subjective loss of energy and inability to perform even simple tasks without exertion. It is the most common complaint of patients seeking general medical care [184, 185]. Fatigue occurs naturally during aging, and it is also an important secondary condition in many clinical illnesses, including respiratory, coronary, musculoskeletal, and bowel conditions as well as infections [184-186].

Chronic Fatigue Syndrome (CFS)

Chronic fatigue lasting more than 6 months that is not reversed by normal sleep along with other signs/symptoms (including neurophysiological) usually indicates CFS [187, 188]. CFS patients also display immune abnormalities, inflammation, autonomic dysfunction and impaired functioning of the hypothalamic-pituitary-adrenal axis [189-191]. This results in alternations in immune cells, such as natural killer cells, and release of pro-inflammatory cytokines [191-195].

Most CFS patients have multiple chronic bacterial and viral infections [196-200]. A common finding was systemic *Mycoplasma* species [197, 200]. For example, when patients were examined for evidence of any multiple, systemic bacterial and viral infections, the odds ratio for this was found to be 18 (CI 95% 8.5-37.9, p<0.001) [197]. In addition to *Mycoplasma* species (OR=13.8, CI 95% 5.8-32.9, p<0.001), co-infections with *C. pneumoniae* (OR=8.6, CI 95% 1.0-71.1, p<0.01) and HHV-6 (OR=4.5, CI 95% 2.0-10.2, p<0.001) were also found [197]. The presence of these infections was also related to the number and severity of signs and symptoms [201]. Similarly, Vojdani et al. also found *Mycoplasma* species in a majority of CFS/ME patients [200], but this has not been seen in all studies [202]. Regional differences may

be important, because when European CFS patients were examined for various *Mycoplasma* species, the most common species found was *M. hominis* [203], whereas in North America the most common species found was *M. pneumoniae* [197, 201].

CFS patients are also often found to be infected with *B. burgdorferi* [204], *C. pneumoniae* [197, 201, 205], cytomegalovirus [206], B19 parvovirus [207] and HHV-6 [197, 201, 208]. However, not all studies on infections in CFS patients have been accurate. A recent finding of a retrovirus (XMRV) in CFS patients has been proven to be an artifact [209].

As with other diseases that show high rates of chronic infections, CFS patients are also dysfunctional in their mitochondria [210, 211]. Studies have shown deficiencies in ATP production [210, 211] and reduced mitochondrial inner membrane potential [212] in white blood cells from CFS patients. Myhill et al. have proposed that CFS patients have basically two types of mitochondrial impairments: substrate or co-factor deficiencies or defects caused by exogenous or endogenous mitochondrial toxic factors [213]. Intracellular infections are likely the most common cause of the latter type of mitochondrial dysfunction.

Fibromyalgia (FM)

FM has many signs and symptoms in common with CFS, such as debilitating fatigue, mood and cognitive changes and sleep disturbances, but FM patients also present with widespread pain and abnormal pain processing [214, 215]. Among the risk factors for FM include genetic predisposition, obesity, allergies, toxins, autoimmune responses, physical trauma and chronic infections [215, 216]. Up to 70% of FM patients are also diagnosed with CFS [217].

As with CFS, a high incidence of chronic bacterial and viral infections have been found in FM patients [2, 215]. Among the most commonly found infections are due to intracellular bacteria, such as *Mycoplasma, Chlamydia, Brucella* and *Borrelia* (reviewed in [215]). Similarly, viral infections have also been noted, such as cytomegalovirus, enteroviruses and HHV-6 (reviewed in [215]). These infections are often found at the same or higher incidence rates as those found in CFS patients.

Autoantibodies are routinely found in FM patients. One study reported thyroid autoantibodies in 41% of FM patients versus 15% of controls [218], and another report indicated 34.4% of FM patients were positive versus 18.8% in controls ($p=0.025$) [219]. Autoantibodies to serotonin were also identified in 74% of 50 patients with FM compared with 6% of 32 controls [220].

As with CFS, FM patients show dysfunctional mitochondria [221, 222]. Excess oxidative stress was indicated by lipid peroxidation in blood mononuclear cells and plasma from FM patients [222]. In addition, reduced inner mitochondrial membrane potential initiating mitophagy and reductions in functional mitochondria were also found, suggesting that oxidative stress and increased mitophagy may play a role in the pathophysiology of FM [222]. Similar to CFS patients, FM patients also show reduced production of ATP but there were also some differences between CFS and FM patients. In FM patients lower levels of citrate synthase and other enzymes and lower amounts of mtDNA were found compared to CFS patients [223].

Consequences of Mitochondrial Dysfunction

Mitochondrial dysfunction arises from an inadequate number of mitochondria within cells, an inability to provide necessary substrates and cofactors to mitochondria, and dysfunction in their electron transport or ATP synthesis machinery. The number and functional status of mitochondria in a cell can be changed by the fusion of partially dysfunctional mitochondria and mixing of undamaged components to improve overall function (mitophagy), the generation of entirely new mitochondria (fission), and the removal and complete degradation of dysfunctional mitochondria (autophagy) [224]. These events are controlled by complex cellular processes that sense the deterioration of mitochondria, such as the loss of inner mitochondrial membrane potential or the activation of certain transcription pathways [225].

The ability of mitochondria to produce high-energy molecules like ATP is directly related to the ability of the electron transport chain to convert the energy of metabolites to transfer electrons to the electron transport chain from NADH and eventually to molecular oxygen while pumping protons from the mitochondrial matrix across the inner mitochondrial membrane to the intermembrane space [225]. This creates a transmembrane proton gradient (Δp) and electrochemical gradient ($\Delta \square_m$) across the mitochondrial inner membrane that is used by ATP synthase to generate ATP [226].

As a consequence of the electron transport process highly reactive free radicals, such as Reactive Oxygen Species (ROS), are produced as a byproduct of oxidative phosphorylation. The main cellular sources of ROS and related Reactive Nitrogen Species (RNS) are mitochondria, and when produced in excess over cellular antioxidant systems these free radicals can damage cellular lipids, proteins and DNA [227-229]. There are cellular mechanisms to neutralize excess ROS/RNS, such as dismutase enzymes and antioxidants [230]. Another mechanism to control the amount of excess ROS is by a controlled leak of protons back across the inner mitochondrial membrane via uncoupling proteins that allow protons to flow against the proton gradient [226, 231].

Excess oxygen consumption, controlled mitochondrial proton leak and resulting ROS production can result in inappropriate damage to mitochondrial membrane lipids [228, 232], such as the very ROS/RNS-sensitive inner mitochondrial phospholipid cardiolipin [232]. Oxidative damage of inner mitochondrial membrane cardiolipin and other membrane phospholipids can result in increased proton and ion leakage across the inner membrane and partial loss of the electrochemical gradient. Cardiolipin is an important component of the electron transport chain, providing stability for the cytochrome/enzyme complexes in the inner mitochondrial membrane [232, 233]. If damaged by ROS/RNS, oxidized cardiolipin results in loss of electron transport function [233].

Antioxidant defenses usually maintain ROS/RNS levels at concentrations that do not result in oxidation of cellular molecules or stimulate adverse events like carcinogenesis [234, 235]. Endogenous cellular antioxidant defenses are essentual for protecting cellular molecules from oxidative damage and are mediated by proteins, such as glutathione peroxidase, catalase and superoxide dismutase, among others [236, 237]. There are also low molecular weight dietary antioxidants that can modify anti-oxidant oxidant balance [238-240]. Some of these dietary antioxidants have been used as natural preventive agents to shift the excess concentrations of

oxidative molecules down to physiological levels that can be maintained by endogenous cellular antioxidant systems [241].

Supplements for Fatigue and and Mitochondrial Dysfunction

Although mild fatigue can be related to psychological disturbances, moderate to severe fatigue is almost always related to loss of mitochondrial function and diminished production of ATP [211, 212]. A number of natural supplements have been used to treat non-psychological fatigue and mitochondrial dysfunction [6, 242-244]. These include supplements containing vitamins, minerals, antioxidants, metabolites, enzyme inhibitors and cofactors, mitochondrial transporters, herbs and membrane phospholipids (Table 1) [6, 243]. Although several natural supplements have been used to reduce fatigue and improve mitochondrial function, few are considered effective [245]. Among the most useful supplements are the following:

Table 1. Relative Incidence of Some Infectious Agents in Patients with Chronic Disease*

	ALS	**MS**	**AD**	**PD**	**ASD**	**CSF**	**FM**
Borrelia spp	++	++	++	+	++	++	++
Chlamyda spp.	+	++++	+++	++	++	++	++
Mycoplasma spp.	+++++	+++	++	++	+++++	+++++	+++++
Brucella spp.	+				+++	++	++
Cytomegalovirus		++	+		++	+	+
HSV -1	+	+++	+++		++		
HSV-2		+			+		
HHV-6	++	+++	++		+++	+++	+++
Heliobacter spp.			++	+++	+	+	+
Other virus/bacteria	+++	+++	++	++	+ ++	++	+++

*Abbreviations: AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; ASD, autism spectrum disorders; CFS, chronic fatigue syndrome; FM, fibromyalgia; HSV, herpes simplex virus; HHV, human herpes virus; MS, multiple sclerosis; PD, Parkinson's disease

Incidence (above controls): -, 0-1%; +, 1-5%; ++, 6-15%; +++, 16-25%; ++++, 26-50%; +++++, 51-90%

L-Carnitine (LC)

LC (3-hydroxy-4-N-trimethylaminobutyrate) is a naturally occurring fatty acid transporter found in all species of mammals that is directly involved in the transport of fatty acids into the mitochondrial matrix for subsequent β-oxidation [246, 247]. It also functions in the removal of excess fatty acyl groups from the body and in the modulation of intracellular Coenzyme A (CoA) homeostatasis [246, 247]. Due to its importance in fatty acid oxidation and CoA and acyl-CoA homeostatasis, LC is usually maintained within relatively narrow concentration limits. It is an important dietary supplement for maintaining optimal LC concentration within cells [246]. Thus LC deficiency disorders are associated with reduced mitochondrial function, insulin resistance and coronary artery disease [248, 249].

The importance of LC in mitochondrial health has spurred the use of LC supplements to potentially improve mitochondrial function and physical performance [250]. The justification is that increased reliance on fat as the principle substrate for energy production during extreme exercise should reduce the need for carbohydrates and delay the depletion of carbohydrate stores. This should increase overall energy production and reduce exercise-induced fatigue. Increased reliance on lipids requires increased levels of LC to transport fatty acids into mitochondria. However, increasing intake of oral LC, even for a few weeks prior to extreme exercise, did not increase skeletal muscle carnitine content, and therefore it is unlikely that increasing LC supplementation alters muscle metabolism during extreme exercise [251].

LC supplementation has been used in disorders that are characterized by low LC concentrations or impaired fatty acid oxidation, such as diabetes, sepsis, renal disease and cardiomyopathy [252]. For example, in patients with congestive heart failure propionyl-LC supplementation resulted in increased peak heart rate (increased mean by 12%), exercise capacity (increased mean by 21%) and peak oxygen consumption (increased mean by 45%) in the treatment group [253].

Since the rate of mitochondrial oxidative phosphorylation naturally declines with age an important anti-aging use of LC has been to increase the rate of mitochondrial oxidative phosphorylation in aged populations. Feeding old rats acetyl-LC was found to reverse age-related decreases in LC levels while increasing fatty acid metabolism. It also reversed the age-related decline in cellular glutathione levels and improved muscle mitochondrial complex IV activity [251].

Dietary supplementation with LC and its various derivatives (up to 2 g per day) is a safe and potentially useful method to increase mitochondrial function [254]. Multiple clinical trials demonstrating its effectiveness in age-related chronic illnesses other than diabetes and cardiovascular diseases have not been conducted. One exception was a randomized, controlled clinical trial on 70 elderly subjects who were treated with LC for 6 months. At the beginning of the trial the aged subjects were generally found to have muscle weakness, decreasing mental health, impaired mobility and poor endurance. By the end of the study the treated group showed significant improvements in physical fatigue, mental fatigue and fatigue severity. They also displayed reductions in total fat mass, increased muscle mass and an increased capacity for physical and cognitive activity through reduced fatigue and improved cognitive function [255]. Other clinical trials on alcoholism, hepatic encephalopathy, coronary heart diseases, Peyronie's disease, cerebral ischemia and infertility indicate that supplementation with LC can have positive effects (reviewed in [254]).

Alpha-Lipoic Acid (ALA)

ALA (1,2-dithiolane-3-pentanoic acid) is a potent antioxidant, transition metal ion chelator, redox transcription regulator and anti-inflammatory agent [257]. ALA acts as a critical cofactor in mitochondrial □-ketoacid dehydrogenases, and it is important molecule in mitochondrial oxidative decarboxylation [257, 258]. Clinically ALA has been used as an oral supplement in the treatment of complications associated with diabetes mellitus, and it has been shown to bring about improvements in various diabetic-associated neuropathies, inflammation and vascular

health [245]. These effects have been attributed mainly to ALA having signal transduction effects on gene regulation and glucose uptake and metabolism [259].

During aging and in many chronic diseases certain sphingolipids, especially ceramides and in particular short-chain ceramides, accumulate in mitochondria due to hydrolysis of sphingomyelin by sphingomyelinase. Eventually this retards electron transport activity [260, 261]. Ceramide accumulation in mitochondria is especially damaging in cardiac tissue, so in aging rodents□ ALA has been used to lower ceramide levels in the vascular endothelial cells of cardiac muscle by inhibiting sphingomyelinase activity. This resulted in restoration of mitochondrial glutathione levels and increasing electron transport function [262].

As previously discussed, in diabetes ALA has been used to reduce diabetic complications, such as sensorimotor polyneuropathies [263]. A blinded study demonstrated its clinical utility with some neuropathic impairments improving significantly on □-Lipoic acid (but not nerve conduction attributes) [264]. The long-term use of ALA has proven to be safe in diabetic patients [264].

Given as an oral supplement ALA is rarely present in tissues above micromolar levels; therefore, it is unlikely to be an important cellular antioxidant [258]. However, an important property of ALA is its ability to increase cellular glutathione levels by regulating glutathione synthesis and thus indirectly reducing oxidative stress [252]. ALA can also modify the regulation of nuclear transcription factor NF-□B, and by doing this it can cause widespread transcriptional effects, resulting in the reduction of free radical and cytotoxic cytokine production [265]. As a transition metal chelater ALA can remove excess copper, iron and other metals that are involved in chronic diseases, such as hemochromatosis, end-stage renal failure, AD and PD, and it is a potential therapeutic agent to prevent or mitigate heavy metal poisoning [256].

ALA has been shown to improve cognitive function along with mitochondrial function, suggesting a link between oxidative damage to mitochondria and congnition [266]. ALA has not been used in clinical trials on chronic fatigue, but its widespread use as a safe supplement (at doses of 200-600 mg/day) to support mitochondrial function and reduce oxidative stress has justified its incorporation into various anti-aging and mitochondrial support supplements [264, 265].

Coenzyme Q10 (CoQ10)

Ubiquinone or CoQ10 is a key mitochondrial cofactor and component of the mitochondrial electron transport chain and one of the most widely used natural supplements [243, 267]. It is also a strong antioxidant in its reduced form, and it can modify the expression of certain genes involved in cell signaling, metabolism and transport [267, 268]. The most important role of CoQ10 is its involvement in the transfer of electrons along the multiple complexes of the mitochondrial electron transport chain [267, 269]. It has been used in doses up to 1,200 mg per day, but most studies used lower doses [267].

CoQ10 is an essential component of the mitochondrial oxidative phosphorylation system, thus its supplementation in patients with reduced CoQ10 levels should result in increased mitochondrial energy production and reduced fatigue [267, 269]. A systematic review of the literature on the effects of CoQ10 on adaptive physical exercise, hypertension and heart failure

revealed that most published studies showed modest improvements in exercise capacity in the subjects given oral CoQ10 [270]. In addition, in eight publications on the effects of CoQ10 on hypertension there was a mean decrease in systolic (-16 mm Hg) and diastolic (-10 mm Hg) blood pressure. In nine randomized trials on the use of CoQ10 in heart failure patients there were non-significant trends towards increased injection fraction and reduced mortality [270]. Rosenfeldt et al. performed their own three-month randomized, placebo-controlled trial on the effects of oral CoQ10 in patients with heart failure [270]. They found that in the test arm but not in the control arm patients showed significant improvements in symptoms and a trend towards improvements in mean exercise times [270].

As mentioned above, the anti-fatigue effects of oral CoQ10 during physical exercise have been examined in a blinded, cross-over trial [271]. Healthy subjects received CoQ10 or placebo for eight days, and their performance was evaluated at fixed workloads on a bicycle ergometer twice for two hr with a four hr rest in-between [271]. The subjects on CoQ10 were able to achieve higher work outputs, they reported less fatigue, and their need for a recovery period was alleviated compared to the placebo group [271]. This study indicated that CoQ10 is a useful supplement to improve fatigue and performance.

In patients with various diagnoses, such as neurodegenerative disease, CoQ10 has been used to reduce symptoms and delay progression [267, 269]. In AD models CoQ10 administration significantly delayed brain atrophy and typical β-amyloid plaque formation [272, 273]. In a randomized, placebo-controlled clinical trial on Alzheimer's patients that took an oral mixture of CoQ10, vitamins C and E and ALA in the test arm showed significant reductions in oxidative stress markers but failed to show significant changes in cerebrospinal fluid markers related to β-amyloid or tau pathology [273]. PD patients generally show increased oxidized-to-total CoQ10 ratios as well as significant increases in markers of oxidative damage in the cerebrospinal fluid, but this can be partially reversed with CoQ10 supplementation [274]. In patients with early Huntington's disease CoQ10 administration for 30 months slowed the usual decline in total functional capacity, but these differences did not reach statistical significance [275]. In contrast, in a multi-center placebo-controlled phase II trial with amyotrophic lateral sclerosis patients CoQ10 did not significantly modify functional decline over a nine-month period [276], and in genetic-based mitochondrial diseases CoQ10 plus several vitamins was shown to be ineffective [277].

Reduced Nicotinamide Adenine Dinucleotide (NADH)

NADH is a cellular redox cofactor in over 200 redox reactions and serves as substrate for certain enzymes [278, 279]. Cells have a universal requirement for NADH, and its deficiency results in a condition called pellagra, which is characterized by dermatitis, diarrhea, dementia and eventually leads to death [279]. In the mitochondria NADH delivers electrons from lipid and other metabolite hydrolysis to the electron transport chain, but in its reduced form NADH can also act as a strong antioxidant [278, 279].

Historically dietary NADH supplementation has been via NADH precursors, such as niacin, nicotinic acid or nicotinamide, but recently microcarriers have been used to stabilize oral NADH so that it can be directly absorbed in the gastrointestinal tract. This turns out to be more effective

than using large oral doses of uncomplexed NADH, which are prone to oxidation and degradation and are generally considered ineffective [280].

In many chronic diseases oxidative damage is extensive, and various mitochondrial antioxidants have been used to treat disease and delay progression [4-6, 243, 281-284]. Nowhere has this been more apparent than in neurodegenerative diseases [4, 5, 84, 86, 134, 239]. For example, in AD stabilized oral NADH has been used to improve cognitive functioning and dementia [278]; however, in another clinical trial there was no evidence of improvements in cognition or dementia using oral NADH [280]. In a controlled clinical trial AD patients were given stabilized NADH or placebo for six months, and it was found that the test group had significantly better performance scores than the placebo group (verbal fluency, visual construction and a trend toward increased performance on abstract verbal reasoning) [285]. However, there was no evidence of better performance using other measures (attention, memory) or on scores of dementia severity [285].

Stabilized oral NADH has also been used to reduce the symptoms of PD. In a preliminary open label clinical trial the effects of IV and oral NADH in over 800 Parkinson disease patients 19.3% of patients showed 30-50% improvement in disability, 58.8% had moderate (10-30%) improvement, and 21.8% did not respond to the therapy ($p<0.01$) [286]. Younger patients with a shorter duration of disease responded better and showed more significant improvements than older patients and patients with a longer duration of disease. The oral form was found to comparable to IV NADH in its effects [286]. However, when this type of trial was repeated statistically significant improvements in PD Rating scores were not found in patients treated with NADH, and diferences were also not found in CSF clinical markers associated with PD severity [287].

Oral NADH has also been used in a stabilized form to reduce symptoms in patients with chronic fatigue. One such study on CFS patients used stabilized, oral NADH or placebo for four weeks in a cross-over trial [288]. Eight of 26 patients (30.7%) responded positively to the microencapsulated NADH compared with 2 of 26 (8%) in the placebo arm ($p<0.05$) [288]. There was clearly an effect but only in a subset of patients in the trial. These results were not considered significant by Colquhoun and Senn [289]. A comparison of oral, stabilized NADH to psychological/nutritional therapy in 31 chronic fatigue syndrome patients revealed that stabilized NADH alone reduced fatigue in the first 4 months of a 12-month trial. After the first 4 months, however, symptom scores were similar in the NADH and the psychological/nutritional arms of the trial [290]. In another study stabilized NADH was given orally for two months to treat CFS patients with extensive fatigue [291]. Alegre et al. found in decreases in anxiety and maximum heart rate after a stress test, but there were little or no differences found in the functional impact of fatigue, quality of life, sleep quality, exercise capacity, or functional reserve [291]. The stabilized NADH alone has shown mixed results in various diseases and disorders, and not every patient responded to the oral, stabilized supplement [6].

Lipid Replacement Theapy (LRT)

The dietary replacement of cellular membrane phospholipids (LRT) using food-derived glyerolphosholipids to remove damaged, mainly oxidized, membrane lipids in mitochondria and other cellular organelles has proved very effective at increasing mitochondrial function and

reducing fatigue [6, 7, 212, 244]. To some degree antioxidant supplements can reduce ROS/RNS levels and prevent some mitochondrial membrane phospholipid oxidation, but antioxidants alone cannot repair the damage already done to cells, and in particular, to their mitochondrial inner membranes [7, 244].

The use of oral membrane phospholipids plus antioxidants in doses ranging from 500-2,000 mg per day has been effective in the treatment of various clinical conditions, such as CFS and other fatiguing illnesses (Table 2) [6, 7, 136, 212, 292, 293]. LRT results in the actual replacement of damaged membrane phospholipids with undamaged (unoxidized) lipids to ensure proper function of cellular and especially mitochondrial membranes. In these studies fatigue was monitored by use of the Piper Fatigue Scale (PFS) to measure clinical fatigue and quality of life [294].

Table 2. A partial list of ingredients/agents or supplements that have been used or suggested to treat mitochondrial dysfuction[1]

Category	*Examples*
Vitamins	Vitamins C, D and E, Thiamine, Riboflavin
Minerals	Magnesium, Calcium, Phosphate
Lipids	Membrane Phospholipids, Unsaturated Fatty Acids
Metabolites	Creatine, Pyruvate
Cofactors	CoQ10, α–Lipoic acid, NADH, nicotinic acid
Transporters	L-Carnitine, Membrane Phospholipids
Antioxidants	CoQ10, α-Lipoic acid, NADH, Glutathione
Enzyme inhibitors	α-Lipoic acid, Dichloroacetate
Herbs	Curcimin, Schisandrin

[1] Modified from Kerr [243] and Nicolson [6]

In a subsequent cross-over study the effects of LRT on fatigue and mitochondrial function were monitored in patients with moderate to severe chronic fatigue [212]. There was good correspondence between reductions in fatigue and gains in mitochondrial function. After 8 weeks of LRT with NTFactor, mitochondrial function was significantly improved, and after 12 weeks of NTFactor supplementation, fatigue was decreased by 35.5% ($p<0.001$), and mitochondrial function was found to be similar to that found in young healthy adults (26.8% increase, $p<0.0001$) [212]. After 12 weeks of supplement use, subjects were placed on placebo for an additional 12 weeks, and their fatigue and mitochondrial function were again measured. After the placebo period, fatigue and mitochondrial function were intermediate between the initial values and those found after 8 or 12 weeks on the supplement, indicating that continued supplementation is required to show improvements in mitochondrial function and maintain lower fatigue scores [212].

Similar findings on fatigue reduction were observed in chronic fatigue syndrome and fibromyalgia syndrome patients given oral membrane phospholipids (NT Factor) [293]. Using a new formulation of NT Factor plus vitamins, minerals and other supplements in patients with

moderate chronic fatigue resulted in a 36.8% reduction in fatigue within one week [295] (Table 3).

Table 3. Effects of Dietary LRT Supplement NTFactor® on Piper Fatigue Scores.[1]

Subjects/patients	n	Av age	Time on LRT	Piper Fatigue Score[2] Fatigue Reduction (%)	Reference
Chronic fatigue[3]	34	50.3	8 wks	40.5**	Ellithorpe et al. [319]
Aging, chronic fatigue[4]	20	68.9	12 wks	35.5*	Agadjanyan et al. [212]
CFS (and/or FM)[3]	15	44.8	8 wks	43.1*	Nicolson & Ellithorpe [293]
Obesity, fatigue[5]	35	42	8 wks	24*	Ellithorpe et al. [318]
Aging, chronic fatigue[6]	67	57.3	1 wk	36.8*	Nicolson et al. [295]
CFS, others[7]	58	55.0	8 wk	30.7*	Nicolson et al. [302]

[1]Modified from Nicolson and Settineri [7]
[2]From Piper et al. [294]
[3]Propax™ with NT Factor®
[4]NT Factor®
[5]Healthy Curb™ with NT Factor®
[6]Advanced Physician's Formula™ with NT Factor®
[7] ATP Fuel® with NTFactor®, CoQ10, NADH, LC, α-keto glutaric acid
**P<0.0001, *P<0.001 compared to without NT Factor®

Vitamins and Minerals

Vitamins, minerals and other small molecules fall into the category of micronutrients. They are essential in the support of mitochondrial function by providing antioxidants, cofactors, metal ions, salts, and other molecules that are essential in supporting the functions of mitochondrial enzymes, electron transport systems, mtDNA replication, fat and sugar metabolism, protein synthesis and proper antioxidant balance [296-298]. Vitamins, such as B (multiple), D, E, C, and ions, such as iron, magnesium, manganese, zinc, among other small molecules, are important n this regard, and up to one-half of the aging North American population is deficient in these vitamins, minerals and other micronutrients [299].

The use of micronutrients in helping to restore and/or maintain mitochondrial function has proven useful in consert with other treatment modialties [296, 298, 300]. Although there are few clinical trials in the literature that demonstrate the usefulness and utility of supplementation with only vitamins, minerals, antioxidants and other micronutrients alone in supporting mitochondrial function, the ones that have been conducted clearly show the importance of providing adequate

oral doses of vitamins, minerals, antioxidants and other micronutrients to maintain mitochondrial energy functions [296. 300-302]. However, their sole use in the treatment of mitochondrial diseases has proved disappointing [277]. But it is reassuring to find that many commercial mitochondrial supplements contain adequate amounts of these important molecules (for example [282, 292, 295, 302]). Thus in addition to vitamins, minerals, antioxidants and other micronutrients, other supplement components are likely required for significant and lasting effects on mitochondrial function.

Combination Supplements to Restore Mitochondrial Function

Oral supplements containing membrane phospholipids (NTFactor, 2,000 mg/day), CoQ10 (35 mg/day), microencapsulated NADH (35 mg/day), LC (160 mg/day), α-ketoglutaric acid (180 mg/day) and other micronutrients have been combined into a dietary supplement (ATP Fuel®) to treat fatigue and mitochondrial dysfunction [303]. This formulation was used in a study to treat long-term intractable fatigue in patients with a variety of diagnoses during a two-month trial.

The 58 participants in the ATP Fuel trial had moderate to severe intractable fatigue for an average >17 years and had been to an average of >15 practitioners without resolution of their fatigue. The study included 30 patients with chronic fatigue syndrome, 17 with chronic Lyme disease; 16 with other fatiguing illnesses, including fibromyalgia syndrome and Gulf War illness; 4 with autoimmune disease, including rheumatoid arthritis; 2 cancer; and 2 diabetes. These patients had tried unsuccessfully many drugs and supplements (average >35) to reduce their fatigue without success [303].

Participants in the trial included chronic illness patients who took the combination LRT supplement (ATP Fuel®) for 8 weeks, and their fatigue was scored monthly [303]. The Piper Fatigue Score (PFS) is a validated instrument that measures four dimensions of subjective fatigue: behavioral/severity, affective/ meaning, sensory, and cognitive/mood [294]. These were used to calculate the four subscale/dimensional scores and the total fatigue scores. In this study the long-term chronic illness patients with intractable fatigue had initial PFS mean total fatigue scores of 7.51 ± 0.29, and after 8 weeks of supplement the mean scores improved to 5.21 ± 0.28, or a 30.7% reduction in fatigue ($p<0.0001$) [303].

The PFS fatigue scores can be further dissected into four subcategories: (i) Behavior/Severity subcategory, which deals with completing tasks, socializing, engaging in sexual activity and other activities, and intensity or degree of fatigue; (ii) Affective/Meaning subcategory, which determines whether the fatigue/tiredness is pleasant/unpleasant, whether the patient is agreeable/disagreeable, protective/destructive, or feels normal/abnormal; (iii) Sensory subcategory, which determines whether the patient is strong/weak, awake/sleepy, refreshed/tired, or energetic/unenergetic; and (iv) Cognitive/Mood subcategory, which assesses whether a patient feels relaxed/tense, exhilarated/depressed, able/unable to concentrate, remember, and think clearly) [294]. All of these fatigue subcategories showed significant reductions by the end of the 8-week trial ($p<0.0001$). For example, there was a 30.7% reduction ($p<0.0001$) in severity/behavior of fatigue, indicating that there was a significant reduction in the intensity of fatigue, and a significant increase in the ability to complete tasks, socialize, and engage in sexual and other activities. Also, there was also a 28.0% improvement ($p<0.0001$) in mood and cognitive ability, such as the ability to concentrate, remember, and think clearly [303].

The benefits of combining various natural mitochondrial support components into combination mitochondrial supplements should be obvious. Separate supplements are no longer required, and the individual components can be adjusted in dosage to provide maximal effectiveness. Also, with combined supplements patients who often have memory and other defects are more likely to be compliant than with the requirement of taking several separate supplements on a daily basis. New formulations can be designed to replace damaged mitochondrial components and also address particular protective needs, such as preconditioning to defend against oxidative stress, damage to ion channels and other needs [304].

Final Comments

There is ample evidence that intracellular infections are linked to mitochondria and mitochondrial dysfunction. Mitochondria play essential roles in cellular homeostasis through control of cell death and as sentinels of cellular danger, such as oxidative stress, loss of essential growth and maintenance factors, physical damage and infection by foreign agents [305-307]. They also orchestrate cellular adaptive danger responses to sustain cell survival, especially when infections threaten cellular systems [307, 308]. However, microorganisms have evolved with different strategies to evade or circumvent host mechanisms to identify, neutralize and degrade them [308-310].

During infection and cellular invasion by microorganisms coordination of multiple innate immune signaling pathways occurs through different pathogen-associated molecular pattern recognition receptors. The recognition of foreign invaders (and other danger molecules) by these innate receptors (Patern Recognition Receptors) can initiate an intracellular signaling cascade that results in activation of anti-microbial mechanisms to clear the infection [311, 312].

Mitochondria have emerged as critical regulators of innate immune responses to invading pathogens as well as other stressors [311-313]. They initiate immune signaling modulators that are tightly linked to mitochondrial energetics through intracellular danger-sensing multiprotein platforms called *inflammasomes* [12, 313, 314]. Thus mitochondria operate as fundamental "hubs" in the pathways from detection of intracellular pathogens to adaptive responses that attempt to neutralize and eliminate pathogens as well as housing crucial signal transducers and providing a structural scaffold that is involved in regulating anti-microbial activities [305, 306]. They also warn the host with danger signals by providing multiple mitochondrial damage products (DAMPS) that are recognized by the innate immune system, resulting in the stimulation of local or systemic immune responses [315].

Mitochondria are addionally implicated in pathways that result in the cellular destruction of pathogens by autophagy through specialized autophagosomes [304, 307]. When pathogens damage cells beyond their ability to be repaired, mitochondria are also involved in initiating and removing the damaged cells by apoptosis [304, 316]. They not only modulate apoptosis triggered by terminal alternations in intracellular homeostasis, but they can also participate in apoptosis stimulated by responses to extracellular or external signals [317, 318]. Thus mitochondria are intrinsically tied to cellular infections in a number of ways.

Oral mitochondrial supplements containing various mitochondrial substrates, cofactors, precursors, components and modulators have proven useful in maintaining and improving mitochondrial function in various chronic diseases. In some examples cited in here this has

resulted in reduction of specific illness signs and symptoms, improvements in quality of life and assistance in over-all recovery. Future efforts to refine and improve oral mitochondrial supplements and apply them clinically should enhance our abilities to treat and care for chronic illness patients as well as improve quality of life for aging populations.

List of Abbreviations Used

AD, Alzheimer's disease; ALA, α–Lipoic acidALS, amyotrophic lateral sclerosis; ASD, autism spectrum disorders; CFS, chronic fatigue syndrome; CI, confidence interval; CMV, cytomegalovirus; CoQ10, coenzyme Q10; CSF, cerebrospinal fluid; CNS, central nervous system; ELISA, enzyme linked immunoabsorbant assay; HHV human herpes virus; HSV, herpes simplex virus; LC, L-carnitine; LRT, Lipid Replacement Therapy; MS, multiple sclerosis; NADH, Reduced Nicotinamide Adenine Dinucleotide;PCR, polymerase chain reaction; PD, Parkinson's disease RNS, Nitrogen Reactive Species; ROS, Reactive Oxygen Species

Competing Interests

The authors have no financial interests or conflicts of interest.

Authors' Contributions

All authors contributed to this review.

Acknowledgements and Funding

The authors would like to thank Nutritional Therapeutics, Inc. and Researched Nutritionals, Inc. for research and clinical trial financial support.

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