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Forum Review

Treating Neurodegeneration by Modifying Mitochondria: Potential Solutions to a "Complex" Problem

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ABSTRACT

Mitochondria function differently in aged brains than they do in young brains. Consistently reported changes include reduced electron transport chain (ETC) enzyme activities, reduced phosphorylation of ADP, and increased reactive oxygen species (ROS) production. Various neurodegenerative diseases are also associated with changes in mitochondrial function, and these changes both recapitulate and extend those seen in "normal" aging. Unfortunately, attempts to treat neurodegenerative diseases by treating mitochondria-related pathology have thus far minimally impacted affected patients. A better understanding of how mitochondrial function changes in aging and neurodegenerative diseases, though, now suggests new approaches to mitochondrial therapy may prove more efficacious. Increasing ETC capacity, increasing oxidative phosphorylation, or decreasing mitochondrial ROS may yet prove useful for the treatment of brain aging and neurodegenerative diseases, and accomplishing this seems increasingly feasible. This review will discuss the role of mitochondrial function and dysfunction in aging and neurodegenerative diseases, and will focus on potential treatment strategies. *Antioxid. Redox Signal.* 9, 1591–1603.

INTRODUCTION

MITOCHONDRIA ARE DYNAMIC ORGANELLES. They house numerous biosynthetic pathways, facilitate energy production, and regulate cell demise. Sophisticated signaling systems have evolved that help mitochondria respond to their host cells and their host cells respond to them. Mitochondria emphasize different roles in different tissues. In neurons, this role is the provision of ATP, which is accomplished through an aerobic process called oxidative phosphorylation. Central to oxidative phosphorylation is a series of multimeric enzyme complexes called the electron transport chain (ETC).

A "mitochondrial theory of aging" derives from data suggesting that ETC activity declines with age, and mitochondrial-based oxidative stress increases with age (10, 23, 66, 95, 110, 112). Some believe a time-dependent accumulation of somatic mitochondrial DNA (mtDNA) mutation also plays an essential role (97, 179). Some permutations of the theory emphasize the importance of reduced oxidative phosphorylation, whereas others emphasize the primacy of oxidative stress (a "free radical theory of aging") (11, 56). The end result, though, is the same. Cells senesce, they age, and then they die.

As is the case with youth versus aging, mitochondria function differently in persons with certain neurodegenerative diseases than they do in persons without such diseases. These functional differences are quantitatively greater than those occurring in healthy older persons (9). Few would argue, therefore, that mitochondrial function in persons with diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD) are normal variations of what would be expected in healthy individuals. For these diseases, it seems appropriate to characterize mitochondria as dysfunctional.

Some argue that neurodegenerative disease-associated mitochondrial dysfunction is etiologically or pathologically irrelevant, and perhaps an artifact. Others feel it may represent an extremely upstream event that actually drives onset and progression of the observed diseases (124). Disagreement on where to place the burden of proof exists. Those who feel mitochon-

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drial function is not important to neurodegenerative diseases with mitochondrial dysfunction demand proof of its phenotypic relevance. Those who believe mitochondrial dysfunction is important request proof of irrelevance.

In some ways, the undisputed fact that mitochondrial dysfunction occurs in patients with certain neurodegenerative diseases appears lost in the debate. Indeed, the mitochondrial theme is generally subservient to other disease-spanning conceptual themes, such as those considering the roles specific protein aggregations play in neurodegenerative diseases. These protein aggregation themes have benefited by inclusively "lumping" all disorders manifesting a particular protein aggregation within a common category. Given such precedent, defining another lumped category, the "neurodegenerative mitochondriopathies", seems reasonable. For a disorder to qualify as a neurodegenerative mitochondriopathy, it is worth considering whether the disorder manifests two requisite core features. Neurodegeneration must occur, and mitochondrial dysfunction must be present. Table 1 identifies several disorders that manifest these features.

This review assumes that mitochondrial dysfunction is relevant to the neurodegenerative mitochondriopathies. Support for this perspective is discussed, as are the possible origins and consequences of mitochondrial dysfunction in neurodegenerative mitochondriopathies. Previously, numerous investigators assuming mitochondria contribute to neurodegenerative diseases have attempted mitochondria-relevant therapeutic interventions. This review will discuss the rationale underlying these attempts, as well as theoretical strategies for treating these diseases by treating their mitochondria. Because substantial data suggest mitochondria play a role in aging, and advancing age is the most profound risk factor for several neurodegenerative diseases, a brief review of the mitochondria-aging nexus is first considered.

THE BRAIN'S MITOCHONDRIA CHANGE AS THE BRAIN AGES

Studies characterizing mitochondrial function in aging brains report several consistent findings. The most solid observations involve reduction of complex I activity, reduction of complex IV activity, and increased production of reactive oxygen species (ROS) (116). Reductions in the number of brain mitochondria do not appear to account for these changes. Therefore, the most reasonable explanation is that physical changes to the enzyme complexes are responsible (126). Other age-related mitochondrial changes include a reduction in membrane potential, increased size, and increased fragility (116).

The mechanisms underlying these functional and structural changes are unproven, but hypotheses exist. Speculation presumes mtDNA mutations cause aberrant production of ETC subunits. Several lines of evidence support this. Deletions of mtDNA accumulate with age in many tissues, especially brain (33). It is easier to find low abundance, heteroplasmic point mutations (microheteroplasmy) in the brains of elderly individuals than in the brains of young individuals (96, 154). The number of microheteroplasmic mtDNA cytochrome oxidase subunit 1 (CO1) gene mutations inversely correlates with cytochrome oxidase activity (96). During aging, activity of an all-nuclear encoded ETC complex, complex II, remains constant (116).

It is unclear whether changes in mitochondrial function promote aging, aging promotes changes in mitochondrial function, or both. Several groups have considered this conundrum and designed experiments testing the relationship between mtDNA, mitochondrial function, and aging. Three laboratories have produced and studied mice expressing altered versions of the mtDNA polymerase γ (mtPOLG) (86, 175, 187). In each case, the alteration involved changes to the proofreading portion of the enzyme, which increases the chance mtDNA will accrue mutations during replication. Although characterizations of brain and brain mitochondria are not published, characterizations of other tissues are available. In general, there is acceleration of mtDNA deletion and point mutation accumulation, an age-dependent progressive reduction of ETC enzyme activities, and accelerated aging (86, 175). One group evaluated oxidative stress markers in its mice, and did not find elevations of the assayed oxidative stress markers (86). One group reported activity of citrate synthase, a mitochondrial matrix enzyme, was elevated (175). Citrate synthase is widely used as a marker of mitochondrial mass. This elevation was felt to perhaps represent a secondary mitochondrial biogenesis.

NEURODEGENERATIVE DISEASES ASSOCIATE WITH MITOCHONDRIAL DYSFUNCTION

For some Mendelian neurodegenerative disorders with known causal gene mutations (Freidreich's ataxia, Wilson's disease, recessive hereditary spastic paraparesis), the corresponding gene product localizes to mitochondria (25, 83, 101). In Huntington's disease (HD), the mutant protein does localize to the mitochondrial outer membrane, but direct effects on mito-

Table 1. Disorders with Neurodegeneration and Electron Transport Chain Defects

Disorder	*Electron transport chain defect*
Alzheimer's disease	Complex IV
Parkinson's disease	Complex I
Amyotrophic lateral sclerosis	Complexes I and IV
Huntington's disease	Complex I, II, III, IV
Progressive supranuclear palsy	Complex I

chondria may not account entirely or at all for ETC dysfunction in this disorder (61, 136). Abundant data also indicate mitochondria are abnormal in the sporadic forms of common degenerations. Complex I dysfunction is associated with Parkinsons's disease (PD), complex IV dysfunction with Alzheimer's disease (AD), and either complex I or IV dysfunction with amyotrophic lateral sclerosis (ALS) (166—168).

The role of ETC dysfunction in sporadic, late-onset neurodegenerative disorders is contentious. Arguments regarding the physiologic importance of ETC dysfunction to these diseases range from pathogenic to epiphenomenal, from pathophysiologically critical to completely irrelevant (168). Data from various investigational lines are used to debate this issue, and results of one investigational line are often used to corroborate or refute those of another. It is therefore worth very briefly reviewing evolution of the mitochondrial debate as it pertains to several representative neurodegenerative diseases.

PD was one of the first identified neurodegenerative mitochondriopathies. Early data supporting a potential role for mitochondrial dysfunction in PD were somewhat fortuitous. In the early 1980s, a toxin-induced subacute parkinsonism syndrome reminiscent of idiopathic PD was described (91). The responsible toxin, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), was next shown to inhibit NADH:ubiquinone oxidoreductase (complex I) following conversion to a related compound, *N*-methyl-4-phenylpyridinium (MPP+) (118). MPTP administration to laboratory animals destroys the substantia nigra and even induces Lewy body formation in aged chimpanzees (50). Subsequent research revealed that other complex I inhibitors induce a parkinsonism phenotype, loss of dopaminergic nigral neurons, and histologic changes similar to those seen in human PD (13, 149).

Realization that complex I inhibition caused a PD-like syndrome heightened the impact of several 1989 reports showing complex I itself is abnormal in PD patients. That year, The Lancet published two letters to the editor showing complex I activity was reduced in both substantia nigra and muscle of those with PD (14, 144). An immunochemical study showed reduced antibody staining of mtDNA-encoded complex I subunit proteins in PD patient basal ganglia (113). The most comprehensive (and first to enter peer review) of the 1989 studies came from Parker *et al*. (122). These authors convincingly showed complex I activity but not other ETC enzyme activities is profoundly reduced in PD patients.

By the end of the 1980s, it was known that complex I dysfunction destroys dopaminergic neurons of the substantia nigra and complex I dysfunction exists in those with idiopathic PD. Some, therefore, considered whether environmental complex I inhibitors might cause PD. This line of research has on several occasions implicated a possible pesticide or herbicide contribution to the PD burden (148). Parker *et al*., meanwhile, proposed mtDNA might account for the PD complex I enzymatic lesion (122). This hypothesis embraced the fact that for most persons with PD the family history suggests a sporadic event and not a Mendelian inheritance pattern. Recognizable autosomal dominant and recessive exceptions to this do exist, but such cases are the minority and serve to demonstrate what we call PD actually consists of numerous, genetically distinct "Parkinson's diseases." Several nuclear gene mutations have in recent years been identified as causes of Mendelian PD, and some of these nuclear genes may also contribute to sporadic PD risk (46, 51, 172). Interestingly, many of these genes encode proteins that localize to mitochondria or which otherwise influence mitochondrial function (1, 59, 88, 160).

The potential contribution of mitochondrial genes to PD's complex I defect, and perhaps to the PD phenotype itself, has been evaluated in different ways. The cytoplasmic hybrid (cybrid) technique has provided one strategy for probing the integrity of mtDNA in PD subjects (164). A general overview of this technique is provided in Fig. 1. The procedure involves ob-

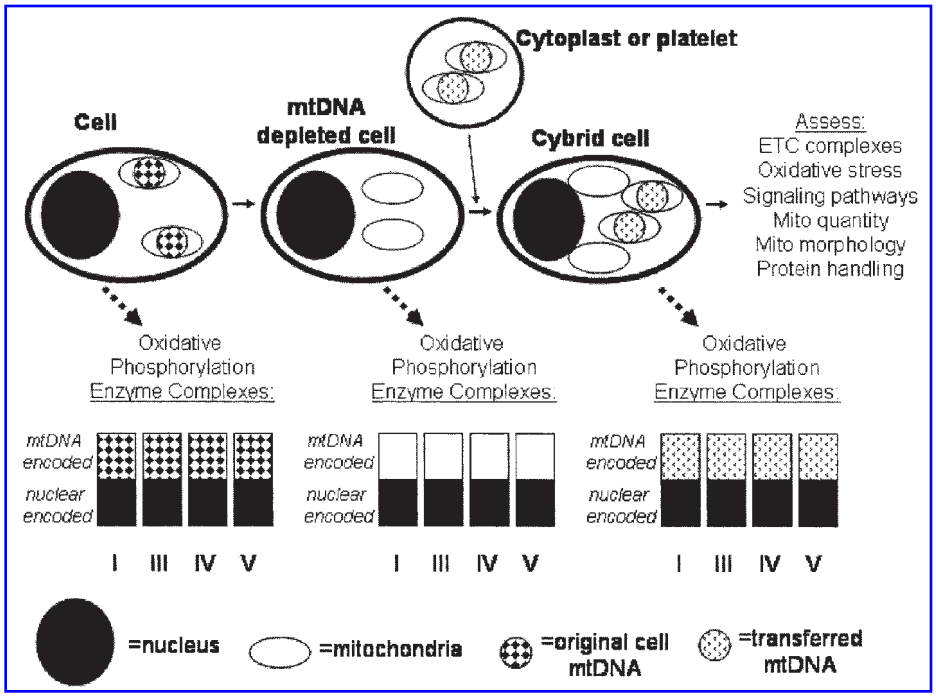

FIG. 1. The cybrid technique. The oxidative phosphorylation complexes I, III. IV, and V are multimeric enzyme complexes containing subunits encoded by both mtDNA and nuclear DNA. Ultimately, mtDNA is the only difference between cybrid cell lines prepared from different mtDNA donor sources. Differences in mtDNA lead to differences in the mtDNA-encoded subunits of these enzymes. Functional differences between cybrid cell lines should reflect differences in mtDNA that cause changes in these enzyme complexes.

taining mtDNA from persons with and without PD. Usually, platelets are used as the mtDNA donor tissue. This is because platelets are easily obtained through standard phlebotomy, easy to isolate through centrifugation, and lack nuclei. Mixing platelets with cell lines depleted of their own endogenous mtDNA allows exchange of platelet and cell line materials. The procedure results in cell lines containing mtDNA from the individual platelet donors. These cell lines expand under standard culture conditions. Their biochemical assessment allows investigators to evaluate parameters directly or indirectly referable to mitochondria and presumably the mtDNA they carry. ETC activities and mitochondrial peroxide production are examples of direct mitochondrial parameters. Indirect parameters include protein aggregation and intracellular signaling pathway alterations, since mitochondrial function may influence such phenomena. To summarize the results of PD cybrid studies, transferring platelet mitochondria to mtDNA-depleted human SH-SY5Y neuroblastoma and human A549 lung carcinoma cells produces cell lines with reduced complex I activity, elevated peroxide levels, increased antioxidant enzyme activities, altered calcium and signaling pathway homeostasis, and cytoplasmic protein aggregations that contain α synuclein. A detailed summary of PD cybrid studies was recently published (170).

If the PD cybrid findings discussed above are truly mtDNA-driven, discerning what makes PD mtDNA unique should be possible. This endeavor is, however, quite complicated. While no simple homoplasmic mutation appears to cause a large number of PD cases, the polymorphic variability of mtDNA sequences from unrelated individuals is enormous. This includes nonsynonymous, synonymous, and regulatory region polymorphisms. The literature is replete with nonsynonymous polymorphism association studies that have reached different conclusions in different populations (166). Part of this discrepancy may result from the possibility that mtDNA polymorphism differences might only cause functionally relevant consequences when expressed against certain nuclear genetic backgrounds (169). Synonymous polymorphisms have received less attention than nonsynonymous polymorphisms, but recent studies showing synonymous polymorphisms can affect protein function may justify a previously unsuspected contribution (79, 82, 115). Recent data also suggest sequence characteristics of the mtDNA D-loop regulatory region can prove clinically relevant to mitochondrial function (34). Therefore, the question of whether homoplasmic mtDNA sequence variability contributes to PD risk remains unanswered.

In addition to the inter-individual homoplasmic variability mtDNA shows, mtDNA sequences within cells may also vary. This phenomenon is called heteroplasmy. Low level heteroplasmies are not detected by standard DNA sequencing approaches (72). More sensitive approaches reveal that mtDNA contains substantial "microheteroplasmies", which can constitute a very low percentage of the mtDNA molecules of a particular tissue or even of a particular cell (24, 96, 111, 154, 158, 159). These heteroplasmies typically consist of either nucleotide substitutions or fairly large deletions. Whether they are inherited or arise somatically is not definitively known. Regardless of how they are introduced into cells, over time clonal expansion of microheteroplasmic mutations within individual cells appears possible (77, 84, 85, 117). Certainly, the overall burden of microheteroplasmic mutations increases with advancing age (96, 111, 154). One laboratory recently reported microheteroplasmic mutations over a limited region of an mtDNA gene, NADH dehydrogenase subunit 5 (ND5), distinguish PD subject brains from those of control subjects (127, 158). This work further revealed the most commonly encountered ND5 PD-associated microheteroplasmic mutations are also found in higher abundance in Leigh's disease (163). Leigh's disease is a disorder of very early childhood, and parkinsonism components are a recognized clinical feature (102).

Because of the well-recognized relationship between ROS levels and mitochondrial function, it is important to note studies of PD brain and peripheral tissues manifest evidence of oxidative stress (17, 41, 73, 108, 129, 131, 137). While a definitive explanation for this finding is currently lacking, the cybrid data discussed above argue overproduction by mitochondria at least partly accounts for increased PD oxidative stress (27, 164). This is consistent with a reported increase in PD brain and peripheral tissue antioxidant enzyme activities (73, 108, 131, 137). However, studies of PD subject brain and peripheral tissues also report antioxidant enzyme activities are decreased or unchanged (3, 39, 80).

Decades of data argue AD subject mitochondria differ from those of non-AD subjects (168). Altered oxidative metabolism in AD brain was noted as far back as 1965 (54). Reports of reduced or altered activity of AD brain mitochondrial matrix enzymes, glycolysis enzymes, and glucose utilization were published starting in the early 1980's (60, 109, 155–157, 161). Also in the 1980s, an avalanche of *in vivo* positron emission tomography studies identified differences between AD and control brain glucose metabolism (45, 52, 53, 55). In 1990, Parker *et al*. reported cytochrome oxidase (complex IV) activity was specifically reduced in platelets from persons with AD (123). This finding was subsequently extended to AD subject brains and fibroblasts (37, 81, 168).

Hirai *et al*. published one of the more detailed histologic analyses of AD brain mitochondria (69). This study found neurons from degeneration-prone regions of the frontal neocortex, temporal neocortex, and hippocampus had reduced numbers of mitochondria. The percentage of cell body space occupied by intact mitochondria was also reduced. However, several other findings indicated despite reduced numbers of intact mitochondria, neurons were actually experiencing mitochondrial proliferation and enhanced mitochondrial turnover. First, there was increased neuronal lipofuscin, potentially representative of increased mitochondrial degradation via lysosomal autophagy (22). Second, there was a striking increase of both deleted and nondeleted neuronal mtDNA. This increase resulted from a profound rise in autophagosome-localized deleted and nondeleted mtDNA. Third, AD neurons actually showed increased CO1 protein levels. Because mitochondrial proliferation appeared not to keep pace with enhanced mitochondrial degradation, the results of this study are consistent with existing data showing cytochrome oxidase activity reductions and reductions in various matrix enzymes (168).

Other AD brain tissue studies similarly report upregulated CO gene expression despite reduced steady-state CO mRNA levels (31, 103). This may cautiously be interpreted as evidence of a functional compensation for declining cytochrome oxidase

activity in surviving neurons (103). A state of concomitantly enhanced mitochondrial proliferation and degradation is further supported by observations that although AD brain has more total mtDNA than control brain (69), AD brain yields reduced amounts of PCR- amplifiable mtDNA (19, 38). Mitochondrial proliferation is also consistent with data derived from mice that express a mutated human amyloid precursor protein transgene. These mice, which also overproduce beta amyloid, show profound early upregulation of nuclear genes that encode key mitochondrial proteins (104, 132).

In addition to finding mtDNA content increased in degeneration-prone neurons in AD brain, Hirai *et al*. also found hippocampal neurons from aged control brains contained more mtDNA than brains from young individuals. Although this rise was not as extensive as what was seen in AD, it is nevertheless important to point out this corroborates the findings of Barrientos *et al*., who also reported neuronal mtDNA content increases with advancing age (8). This places mtDNA levels within the context of an aging-AD continuum. Analysis of AD cybrids also is consistent with the mitochondrial proliferation observed by Hirai *et al*. With successive passage, SH-SY5Y cybrids expressing AD subject mtDNA show increased mtDNA levels, increased mitochondrial numbers, and also a vastly increased percentage of morphologically abnormal mitochondria (176).

Results from AD cybrid studies were summarized in a recent review (170). Briefly, AD cybrid studies in which AD subject platelet mtDNA was expressed within human neuroblastoma SH-SY5Y or human teratocarcinoma NT2 cells reveal reduced cytochrome oxidase activity (despite increased mtDNA levels), increased peroxide levels, increased antioxidant enzyme activities, altered calcium and signaling pathway homeostasis, and extracellular protein aggregations that stain with antibodies to beta amyloid.

As is the case with PD, sequence-level analysis for specific AD mtDNA aberrations is a complicated endeavor. To date, it appears that particular homoplasmic mtDNA mutations are associated with AD in only a very limited number of cases (64). Some reported mtDNA polymorphism associations have not replicated in confirmatory studies, although different studies of particular polymorphisms have used different populations (168). An increasing number of studies have taken the view that mtDNA polymorphisms or haplogroups, while not determinant for AD, still influence AD risk (30, 177). Data from one study cataloging mtDNA CO gene microheteroplasmic mutations was confounded by nuclear pseudogene contamination and subsequently retracted (38). An in-depth study of CO1 microheteroplasmy reported CO1 microheteroplasmic mutations increase with age, correlate with reduced cytochrome oxidase activity, but do not distinguish AD brains from aged control brains (96). There are currently no well-done published assessments of CO2 or CO3 microheteroplasmy. One study evaluating D-loop microheteroplasmy did report mutations in this region were increased in AD and could distinguish AD brains from control brains (34). This potentially important study awaits replication.

Studies of AD brain and peripheral tissue show evidence of oxidative stress (17, 28, 107). A definitive explanation for this finding is currently lacking. The cybrid data discussed above argue mitochondrial overproduction at least partly accounts for increased oxidative stress in AD (170). As is the case with PD, the results of antioxidant enzyme studies in brain and peripheral tissues from AD patients are discordant. Various studies using brain or peripheral tissues report increases, decreases, or no changes in commonly measured antioxidant enzyme activities (16, 17, 28, 80, 98, 106, 107).

Unlike PD and AD, HD is strictly an autosomal dominant disorder. Its ultimate cause is polyglutamine expansion of the huntingtin gene on chromosome 4. The nature of mitochondrial dysfunction in HD may be tissue dependent. The most consistently noted brain ETC defects involve complexes II, III, and IV, while complex I dysfunction is noted in platelets and muscle (5, 18, 20, 62, 125). The mechanisms through which this polyglutamine expansion causes mitochondrial dysfunction are not entirely settled. One hypothesis suggests mutant huntingtin directly interacts with mitochondria, thereby interfering with calcium homeostasis (32, 121). Another hypothesis posits mutant huntingtin disrupts the peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1a) dependent transcription apparatus required for successful mitochondrial biogenesis to occur (36, 162, 182). Regardless, by this review's definition, the presence of mitochondrial dysfunction in HD qualifies this disorder as a neurodegenerative mitochondriopathy.

Markers of oxidative stress are enhanced in HD brains. Increased oxidative modification of cell protein, lipid, and DNA constituents is observed (21). Surprisingly few studies, though, detail the status of HD subject antioxidant enzyme activities. One study of HD brain found glutathione peroxidase activity was neither increased nor decreased in HD brain (80). Erythrocytes from HD subjects, though, were found to have decreased superoxide dismutase, catalase, glutathione reductase, and glutathione peroxidase activities (87).

When data addressing mitochondrial dysfunction in PD, AD, and HD are considered, both common themes and unique features emerge. Mitochondrial dysfunction in all three disorders occurs outside the brain and manifests as decreased ETC capability. In all three disorders, mitochondrial dysfunction correlates with increased brain oxidative stress. On the other hand, the actual ETC defect observed in each of these disorders differs. Complex I activity is reduced in PD, complex IV activity is reduced in AD, and multiple ETC complex activities are reduced in HD. Also, although not definitively settled at this time, antioxidant enzyme status may vary between these disorders.

ATTEMPTS TO TREAT MITOCHONDRIA IN NEURODEGENERATIVE DISEASES

"Mitochondrial medicine" is a relatively young field (100). It has largely developed through experimentation with the mitochondrial encephalomyopathy disorders. Most strategies involve attempts to improve a mitochondrial parameter by providing supplements that theoretically could augment a particular aspect of mitochondrial dysfunction. For example, thiamine and lipoic acid serve as cofactors to some mitochondrial enzymes, such as pyruvate dehydrogenase complex. Dichloracetate stimulates activity of pyruvate dehydrogenase complex, and can reduce lactic acidemia in mitochondrial encephalomyopathy, lactic acidosis, and stroke (MELAS) (138). Attempts to supplement the ETC sometimes include combination approaches, such as us-

ing menadione, which can accept electrons from complex I, with ascorbate, which can donate electrons to complex IV. Nicotinamide has been used in an attempt to increase NADH reducing equivalents, and succinate donates electrons to complex II. Riboflavin is a precursor of the flavin-based electron acceptors FADH2 and FMN.

Although anecdotal reports of therapeutic success are found in the literature, the overall consensus is that classic encephalomyopathies generally show no to minimal response with these interventions (140). For example, while dichloroacetate can reduce lactic acidemia in MELAS, this does not correlate with clinical improvement (141). To a lesser degree, the strategies described above have been attempted in non-encephalomyopathy disorders that may otherwise have a mitochondrial contribution. Migraine is such an example. Some postulate mitochondria may play an important role in migraine, as mitochondrial encephalomyopathy disorders can be associated with migraine headaches, and altered cortical energy metabolism has been reported in individuals with certain migraine types (6, 181). Accordingly, one study found 400 mg per day of riboflavin reduced migraine intensity and onset frequency (145). Regarding the neurodegenerative mitochondriopathies, NADH supplementation was evaluated in PD. Although initial open label studies reported efficacy, placebo-controlled trials produced unimpressive results (165).

Creatine has been considered for the treatment of neurodegenerative mitochondriopathies (171). Creatine is converted by creatine kinase to creatine phosphate, which can serve as a high-energy phosphate reservoir for rapid ATP production. Increasing creatine levels via supplementation conceptually could confer bioenergetic benefits. To date, creatine has been tried in three neurodegenerative mitochondriopathies, ALS, HD, and PD. Results from the ALS and HD trials revealed no evidence of either symptomatic improvement or slowed decline (147, 178). Two PD trials could not rule out the possibility those receiving creatine experienced a slowed rate of decline (12, 119).

The use of antioxidants for the prevention and treatment of neurodegenerative mitochondriopathies has received much attention. Some epidemiologic surveys suggest increased intake of standard antioxidant vitamins (including vitamin E, vitamin C, and beta carotene) might reduce the risk of developing AD or PD, while others do not (43, 44, 92, 99, 186). The fact that different studies reach different conclusions suggests that if there is a protective benefit, it is probably very minor. Similarly, high dose (2,000 units per day of vitamin E) in mild cognitive impairment (often an AD precursor state), AD, and PD show at worst no and at best minimal benefits (128, 130, 139). Thus, it appears antioxidants not targeting specific ROS production sites are unlikely to play a major role in prevention or treatment of neurodegenerative mitochondriopathies.

Coenzyme Q (CoQ) can also serve as an antioxidant, and may prove better for reducing mitochondrial oxidative stress than other antioxidants. CoQ transfers electrons from complexes I and II of the ETC to complex III. It has been studied to some extent in the classic encephalomyopathies, with anecdotal but no generally recognized degree of success (71, 141). A phase II safety trial of CoQ in PD reported that compared to patients on placebo, subjects receiving 1,200 mg per day showed slowed decline over the 16-month trial period (152). A small 6-month trial of lower CoQ doses in HD did not show a clinical benefit (47). A recently completed 4-year, open label trial of CoQ in Friedreich's ataxia reported that for some clinical indices, patients receiving 400 mg per day (in conjunction with 2,100 units per day of vitamin E) declined slightly more slowly than historical cohorts (67). Cardiac benefits were also reported in this open label trial. Additional Friedreich's ataxia CoQ trials report cardiac benefits but not neurologic benefits (185). While there are no published trials of CoQ in AD, idebenone (a water-soluble analog of CoQ) has been evaluated in AD. In the largest of these trials, cognitive decline, as measured by the Alzheimer's Disease Assessment Scale-cognitive subcomponent (ADAS-cog), was reduced over a 1-year period (174). Those receiving idebenone (360, 720, or 1080 mg per day) declined 4.4 points on the ADAS-cog, compared to 6.3 points for the placebo group. However, no benefit for another scale, the Clinical Global Impression of Change (CGIC), was seen. Development of idebenone for AD treatment was therefore abandoned. Despite the mixed data for CoQ or its analogues in human trials, further studies seem warranted, especially since data indicate humans can tolerate doses higher than those previously studied. Mostly minor side effects are observed over 1 month of 2,400 mg per day exposure; higher doses do not further increase serum levels (153).

A new generation of mitochondria-targeted antioxidants is currently in development (2, 133). Sophisticated *in vitro* approaches for repairing mtDNA defects and using mitochondria to house transgenes as part of an overall gene therapy strategy have tremendous translational potential (63, 76, 173).

Whether more potent antioxidants will prove efficacious in the treatment of aging or neurodegenerative diseases remains to be proven or disproven. If free radicals in these conditions induce cell damage independently of the underlying defect(s) giving rise to their overproduction, rational antioxidant therapies may provide some benefit. It is important to keep in mind, though, that oxidative stress arises as a consequence of and serves as a marker of more basic pathology. For situations in which the primary defect involves a mitochondrial enzyme or enzyme complex, effective treatment may require correction of the primary biochemical lesion. With the neurodegenerative mitochondriopathies, there are data suggesting reduced bioenergetic capacity may represent a primary or at least very upstream biochemical lesion (170).

It also appears that, at least in some cases, mitochondrial biogenesis may accompany reduced bioenergetic capacity (8, 69, 175, 176). This relationship suggests mitochondrial biogenesis may represent an attempt to maintain aerobic homeostasis. Since it is possible to experimentally induce mitochondrial biogenesis, mitochondrial biogenesis induction may offer a useful neurodegenerative mitochondriopathy treatment strategy.

Figure 2 summarizes the various approaches considered for the treatment of mitochondrial dysfunction and its consequences. It is important to emphasize that with perhaps minor exceptions, recommending any of the mitochondrial medicine approaches discussed above for the treatment of neurodegenerative diseases is currently unjustified.

MITOCHONDRIAL BIOGENESIS IS A DYNAMIC PROCESS

Cells alter their mitochondrial content contingent on their situation or environment (93). When cells require energy, they

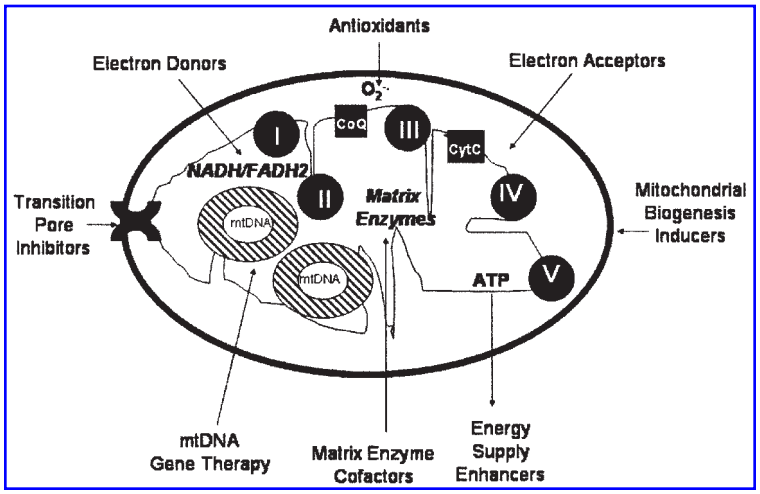

FIG. 2. Mitochondrial medicine targets. I = complex I; II = complex II; III = complex III; IV = complex IV; CoQ = coenzyme Q; CytC = cytochrome C; $O_2^{-\cdot}$ = superoxide radical.

can upregulate their mitochondrial mass. Finding increased citrate synthase in mtDNA hypermutator mice is therefore not surprising (175). Data from aged human brain further show mtDNA content is increased in brains from elderly individuals (8). This mtDNA increase occurs concomitantly with a steady state decrease in mitochondria-relevant mRNA levels. Presumably, increased mtDNA levels in aging brain are a compensatory response to a flexible age-associated, mitochondria-dependent parameter. Some propose increased mitochondrial peroxide production may constitute that parameter (93).

Three high profile inducers of mitochondrial biogenesis include caloric restriction, resveratrol, and exercise. Caloric restriction increases eNOS expression, nitric oxide (NO) levels, and cyclic GMP (120). The resultant mitochondrial biogenesis is associated with increased oxygen consumption and sirtuin 1 expression. Sirtuin 1, an NAD-dependent histone deacetylase homolog of yeast Sir2, benefits cells exposed to stress conditions (4). In rats, caloric restriction increases brain mtDNA levels (26). Sirtuin 1 expression is also promoted by resveratrol (89). In general, resveratrol alters numerous cell parameters in ways similar to those resulting from caloric restriction. With exercise, declining ATP:ADP ratios are associated with increased AMP levels, which activates AMP-activated protein kinase (AMPK). Activation of AMPK is associated with mitochondrial proliferation (29). Drugs that activate AMPK induce mitochondrial biogenesis (29). Alterations of calcium-regulated signaling pathways may also mediate the ability of exercise to induce mitochondrial biogenesis (183).

Although exact mechanisms underlying mitochondrial biogenesis may vary between tissues, emerging data indicate major commonalities exist. Recently, PGC-1a has emerged as a mitochondrial biogenesis master regulator. PGC-1a coordinates a number of metabolically relevant transcription factors (65, 70). It is highly expressed in brown adipose tissue, skeletal muscle, and brain. Nuclear respiratory factor 1 (NRF1) and nuclear respiratory factor 2 (NRF2) are two PGC-1a coactivated transcription factors. Their activation leads to coordinated expression of genes encoding mitochondrial proteins (142). Part of this coordination includes expression of mitochondrial transcription factor A (TFAM), which increases levels and expression of mtDNA (74, 143). It is perhaps through the ability of PGC-1a to exquisitely coordinate expression of two genomes (the nuclear and mitochondrial) that mitochondrial biogenesis can produce functional mitochondria. PGC-1a also activates antioxidant enzyme expression (162).

PHARMACOLOGIC INDUCTION OF MITOCHONDRIAL BIOGENESIS

Resveratrol represents one option for inducing mitochondrial biogenesis (89). The thiazolidinedione drugs constitute another category of drugs that appear to promote mitochondrial biogenesis in neuronal-like cells (58). Thiazolidinediones are currently used clinically to reduce insulin resistance in type II diabetics (184). Reduction of insulin resistance is presumed to result from activation of peroxisome proliferator-activated receptor γ (PPARG). PPARG belongs to a broader family of PPAR nuclear receptors (94, 146). When bound by a coactivator, it promotes expression of genes required for peroxisomal fatty acid β oxidation. It also plays a role in adipocyte differentiation. PPARG's natural coactivator is PGC-1a. Thiazolidinediones thus mimic the effects of PGC-1a on PPARG.

Thiazolidinediones also have mitochondrial effects. It is worth considering whether these mitochondrial effects affect glucose homeostasis in diabetics. Data suggest thiazolidinediones directly affect mitochondrial function by altering ETC coupling—uncoupling (40, 42, 75, 150). These drugs appear to decrease oxidative phosphorylation coupling, which could in turn increase glucose utilization and influence free radical production/oxidative stress. The effects of thiazolidinediones on oxidative stress are difficult to predict. Uncoupling can be associated with reduced free radical production (49). On the other hand, the ability of acute thiazolidinedione exposure to increase oxidative stress has been reported (151). To complicate matters, thiazolidinediones may affect mitochondria through more than one mechanism (48).

Based on real time PCR analysis of mtDNA quantity and expression of nuclear-encoded, mitochondria-relevant genes, it was previously concluded that chronic pioglitazone exposure induces mitochondrial biogenesis in human subcutaneous adipose tissue (15). Chronic pioglitazone exposures induce mitochondrial biogenesis in human neuronal-like NT2 cells (58).

PPARa agonists also reportedly induce mitochondrial biogenesis (105).

The clinically available thiazolidinedione drugs include pioglitazone and rosiglitazone. Despite the fact that they poorly cross the blood-brain barrier, these drugs are under consideration for the treatment of neurodegenerative diseases such as AD (57, 68, 90, 134, 180). The most proposed rationale is thiazolidinedione anti-inflammatory properties may mitigate beta amyloid-induced microglial activation, a process potentially contributing to neurodegeneration (90). Reduced insulin production has also been considered as a potential mediator of any beneficial effects (35). More recently, it was proposed thiazolidinedione mitochondrial effects might benefit AD patients (58, 135).

MITOCHONDRIAL BIOGENESIS FOR THE AGING OR DEGENERATING BRAIN?

For neurodegenerative mitochondriopathies with perturbed mitochondrial proliferation, therapeutic induction of mitochondrial biogenesis seems particularly attractive. As discussed above, HD may represent one such disorder. Increasing PGC-1a expression appears to benefit HD transgenic mice (36).

Inducing biogenesis of already dysfunctional mitochondria is a risky proposition. Doing so could possibly worsen an already unstable situation. On the other hand, in encephalomyopathies, aging, and AD, mitochondrial biogenesis already occurs (8, 69, 93, 114). Perhaps it represents a counter-response to falling or failed aerobic capacity. Theoretically, enhancing this compensatory response could prove therapeutically useful.

When it comes to the treatment of mitochondrial dysfunction, we truly stand at a philosophical fork in the road. Should we focus on minimizing the downstream effects of altered mitochondrial function, or should we enhance those effects? For example, it was previously shown mitochondrial ROS activate potentially protective heat shock proteins (7). In general, reactive oxygen and nitrogen species promote mitochondrial biogenesis (93, 120). The possibility antioxidants might blunt compensatory responses to aerobic decline (failing ETC-dependent oxidative phosphorylation) warrants consideration. To date, most attempts at treating neurodegenerative mitochondriopathies have concentrated on minimizing potentially compensatory events. Recently, though, attempts at maximizing potentially compensatory events have been considered for treatment of a neurodegenerative mitochondriopathy (78).

CONCLUSIONS

For numerous neurodegenerative diseases, mitochondrial dysfunction represents a common event. Using this unifying feature to define a subset of neurodegenerative disorders, the neurodegenerative mitochondriopathies, seems reasonable. Mitochondrial defects in the neurodegenerative mitochondriopathies recapitulate age-associated mitochondrial changes, but are quantitatively greater than those that occur in disease-free aging. This suggests a youth–aging–neurodegenerative disease continuum. Either the process influencing this continuum alters mitochondrial physiology, or else mitochondria themselves mediate the continuum. The presence of mitochondrial dysfunction in nondegenerating tissues in these disorders and the results of mtDNA hypermutator mouse studies are more consistent with the latter scenario than the former.

If the actions of mitochondria indeed contribute to aging and neurodegeneration, which available data argue is likely the case, mitochondria are valid therapeutic targets. Initial attempts using mitochondrial medicine to treat neurodegenerative mitochondriopathies has not been effective to date. However, these attempts have largely focused on minimizing the downstream effects of bioenergetic dysfunction, and these downstream effects may represent a compensatory response to failing aerobic metabolism. Minimization of compensatory responses may yield minimal benefits, especially if approaches for doing so do not address an underlying basic mitochondrial pathophysiology.

For at least some of the neurodegenerative mitochondriopathies, the underlying mitochondrial pathophysiology seems to involve declining aerobic capacity. Declining aerobic capacity in these cases possibly arises secondary to defects in ETC enzyme complexes. Increasing bioenergetic capacity by inducing or enhancing mitochondrial biogenesis may offer one strategy for mitigating ETC enzyme complex problems. Pharmacologic induction of mitochondrial biogenesis is already possible, and further preclinical research into this general approach should aid in the planning of human trials.

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ABBREVIATIONS

AD, Alzheimer's disease; ADAS-cog, Alzheimer's Disease Assessment Scale, cognitive subcomponent; ALS, amyotrophic lateral sclerosis; AMPK, AMP-activated protein kinase; CGIC, Clinical Global Impression of Change; CoQ, coenzyme Q; CO, cytochrome oxidase; ETC, electron transport chain; HD, Huntington's disease; MELAS, mitochondrial encephalomyopathy, lactic acidosis, and stroke; MPP+, *N*-methyl-4-phenylpyridium; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; mtDNA, mitochondrial DNA; mtPOLG, mtDNA polymerase γ; ND, NADH dehydrogenase; NO, nitric oxide; NRF, nuclear respiratory factor; PD, Parkinson's disease; PGC-1a, peroxisome proliferators-activated receptor γ coactivator 1α; PPAR, peroxisome proliferators-activated receptor; ROS, reactive oxygen species; TFAM, mtDNA transcription factor A.

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