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SYMPOSIUM: Mitochondrial Encephalomyopathies

The Role of Mitochondria in the Pathogenesis of Neurodegenerative Diseases

Giovanni Manfredi MD, PhD, and M. Flint Beal, M.D.

Department of Neurology and Neuroscience, Weill Medical College of Cornell University and the New York Hospital- Cornell Medical Center, New York, NY

A growing body of evidence indicates that mitochondrial dysfunction may play an important role in the pathogenesis of many neurodegenerative disorders. Because mitochondrial metabolism is not only the principal source of high energy intermediates, but also of free radicals, it has been suggested that inherited or acquired mitochondrial defects could be the cause of neuronal degeneration as a consequence of energy defects and oxidative damage. Mitochondrial respiratory chain dysfunction has been reported in association with primary mitochondrial DNA abnormalities, and also as a consequence of mutations in nuclear genes directly involved in mitochondrial functions, such as SURF1, frataxin, and paraplegin.

Defects of oxidative phosphorylation and increased free radical production have also been observed in diseases that are not due to primary mitochondrial abnormalities. In these cases, the mitochondrial dysfunction is likely to be an epiphenomenon, which, nevertheless, could be of importance in precipitating a cascade of events leading to cell death. In either case, understanding the role of mitochondria in the pathogenesis of neurodegenerative diseases could be important for the development of therapeutic strategies in these disorders.

Introduction

Neurodegenerative diseases are a clinically heterogeneous group of disorders, which share in common a selective loss of specific populations of neurons. The genetic causes of some of these disorders have been recently elucidated, as, for example, in the case of Huntington disease, Friedreich's ataxia, some forms of familial amyotrophic lateral sclerosis, familial Parkinson's disease, and familial Alzheimer's disease. Despite the obvious differences in their primary etiologies, a role for mitochondrial dysfunction has been postulated in the pathogenesis of these diseases.

Mitochondria are the "power house of the cell", in which metabolites are converted into ATP through oxidative phosphorylation (OXPHOS). Therefore, mitochondrial dysfunction leads to decreased ATP production in the first place, but it also causes other potentially detrimental effects, such as impaired intracellular calcium buffering and the generation of reactive oxygen species (ROS). Theoretically, all these factors can have an important role in causing neuronal death. Mitochondria are also essential in activating certain forms of apoptosis (101). Although a decrease in mitochondrial membrane potential ($\Delta\Psi m$) has been observed in the early phases of apoptosis (109), it is still not clear if decreased $\Delta\Psi m$ due to OXPHOS defects is sufficient *per se* to induce apoptosis.

Mitochondria are under the control of two genomes. They possess their own DNA (mtDNA), which is inherited through the maternal line alone. The mtDNA encodes for 13 polypeptides, all of which are components of the respiratory chain, and for a complement of rRNAs and tRNAs necessary for intra-organellar protein synthesis (98). Although most mitochondrial constituents are encoded by nuclear DNA, mtDNA defects can cause numerous diseases, many of which are associated with neuronal degeneration.

In this review, we will summarize evidence supporting the involvement of mitochondrial impairment in the pathogenesis of paradigmatic examples of neurodegeneration (Table 1). We will first analyze pathologies in which genetic alterations of the mtDNA and ensuing OXPHOS defects are primarily responsible for the dis-

Corresponding author:
Giovanni Manfredi MD, PhD, Assistant Professor of Neuroscience, Weill Medical College of Cornell University, 525 E 68th Street, A-505, New York, NY 10021, USA; Tel.: 212-746-4605; Fax: 212-746-4803; E-mail: gim2004@mail.med.cornell.edu

Examples of neurodegeneration and mitochondrial dysfunction due to:	Mutated gene
primary mtDNA mutations	
Narp/Leigh's syndrome	MtDNA ATPase 6
LHON/Parkinson/dystonia	MtDNA Complex I subunits
Nuclear gene mutations affecting OXPHOS	
Leigh's syndrome (with COX deficiency)	Surf 1 (yeast SHY-1 homologue)
Leigh's syndrome (with COX deficiency)	Sco 2
X-linked Leigh's syndrome (with PDH deficiecy)	PDH
Leigh's syndrome (with Complex II deficiency)	SDH flavoprotein
Leigh's syndrome (with Complex I deficiency)	Complex I subunits
Nuclear gene mutations affecting mitochondrial proteins	
Hereditary spastic paraplegia	Paraplegin
Friedreich's ataxia	Frataxin
Wilson's disease	ATP 7B
Mohr-Tranebjaerg syndrome	DPPI (yeast tim8 homologue)
Mutations of non-mitochondrial proteins	
Huntington's disease	Huntingtin
Amyotrophic lateral sclerosis	SOD-1
Progressive supranuclear palsy	Tau protein
Putative secondary mitochondrial involvement	
Parkinson's disease	unknown
Sporadic Alzheimer's disease	unknown

Table 1. Neurodegenerative disorders with mitochondrial involvement.

eases. We will also look at diseases where nuclear gene defects are the direct cause of OXPHOS impairment and neurodegeneration. We will then describe examples of defects of nuclear-encoded mitochondrial proteins, which cause neurodegeneration, but do not directly participate in OXPHOS functions. Finally, we will summarize the evidence for the involvement of mitochondrial dysfunction and mtDNA alterations in the pathogenesis of disorders, whose genetic causes are still unknown or which are due to mutations in non-mitochondrial proteins.

Neurodegeneration due to primary mtDNA mutations

One of the main clinical characteristics of disorders due to mtDNA abnormalities is the great variability of symptoms associated with any specific mutation. Most of these disorders are multisystemic, affecting tissues and organs differently depending on the metabolic threshold for OXPHOS impairment and on the mutation load.

Among a large number of mtDNA alterations, which are generally loosely associated with specific combinations of symptoms, there are some examples of mtDNA mutations that tend to cause rather selective neuronal degeneration. This situation applies, for example, to mutations in the mtDNA genes coding for ATPase 6 and for complex I subunits.

NARP/Leigh's syndrome. Mutations in the mtDNA ATPase 6 gene have been associated with a syndrome clinically characterized by neuropathy ataxia and retinitis pigmentosa (NARP). The first mutation reported was a T→G transversion at nucleotide 8993 (46). It was later demonstrated that, when the mutation reaches high levels in the brain, the clinical presentation of the disease is earlier and more severe, with a form of subacute necrotizing encephalopathy with clinical and pathological features of Leigh's syndrome (85, 102). The T8993G mutation changes a highly conserved leucine for arginine in the ATPase 6 subunit, presumably impairing the proton flow from the cytosolic to the matrix side of the inner mitochondrial membrane (7). Studies of the mutation on cultured cells have demonstrated a defect of mitochondrial ATP synthesis of variable degree according to the cell type analyzed and the proportion of mutant mtDNA harbored by the cells (66, 103, 108). Other, more rare, pathogenic point mutations have been identified in ATPase 6 in association with Leigh's syn-

drome and bilateral striatal necrosis, among which a T→C transition at nucleotide 8993 (31, 85) and a T→C transition at nucleotide 9176 (20).

Leber's optic atrophy/Dystonia. Three primary point mutations have been specifically associated with Leber's hereditary optic neuropathy (LHON), a subacute degeneration of the optic nerve, that affects especially young males, causing bilateral visual failure and leading to almost complete blindness. They are missense mutations in three complex I subunits, ND1 (nucleotide 3460 (47)), ND4 (nucleotide 11778 (110)), and ND6 (nucleotide 14484 (51)). The G→A transition at nucleotide 3460 causes a marked decrease in complex I activity in cultured cells and in platelets of affected patients (65). The 11778 G→A transition causes a much milder complex I deficiency in patient's platelets (91), but a clear defect in complex I-driven cell respiration has been demonstrated in transmitochondrial cybrids (45). A mild reduction in complex I activity has also been found in leucocytes from individuals harboring the 14484 T→C (78). Other mutations in complex I genes are associated with a "LHON-plus" syndrome. A G→A transition at nucleotide 14459 in ND6 has been identified in familial cases of LHON and dystonia, characterized pathologically by basal ganglia degeneration (52). Another G→A transition at nucleotide 11696 in ND 4, has been found in another family with LHON and dystonia (32). In this family, however, an additional base change, a homoplasmic T→A transition at nucleotide 14596, was also identified, suggesting that in some cases the phenotypic effect of primary mutations could be modulated by "secondary" ones. The 11778 G→A transition has also been identified in a family with maternally inherited, levodopa-responsive parkinsonism (90).

The prevalence of LHON in males is at least 7 to 8-fold greater than in females (75). This has led to the idea that an X-linked genetic defect could play a role in the clinical expression of the disorder. This hypothesis implies that a locus responsible for visual loss on the X chromosome acts in synergism with the mtDNA mutations. In this case, only females homozygous for the disease locus or with inappropriate X inactivation would become affected (18). However, despite extensive efforts, the search for the visual loss locus and for unbalanced X inactivation has thus far been fruitless. Environmental factors, such as alcohol and tobacco, have also been invoked to explain the apparent discrepancies between genotype and phenotype in LHON families (reviewed by Chalmers and Shapira (25)).

Nuclear gene mutations affecting OXPHOS

Leigh's syndrome. Leigh syndrome (LS, MIM 256000) is a severe neurodegenerative condition pathologically characterized by subacute symmetrical necrotic lesions in the subcortical regions of the central nervous system including basal ganglia, thalamus, brainstem, and spinal cord. Demyelination, vascular proliferation, and gliosis are also part of the pathologic picture. Onset is most frequently in early infancy but may sometimes be in adult life. Symptoms include motor and mental regression, ataxia, dystonia, and abnormal breathing. Death generally occurs within two years after onset.

LS is due to impaired mitochondrial energy metabolism, which can derive from a variety of molecular defects. In some cases, when the mutational load is high, mtDNA mutations in the ATPase6 gene (see above) are responsible for maternally inherited LS (MILS). Inheritance of LS can also be X-linked or recessive. A study of the genetic causes of LS in a large group of patients showed that approximately 19% of cases were due to mtDNA mutations, and 10% to X-linked pyruvate dehydrogenase complex (PDHC) defects. The remaining 71% were due to a variety of autosomal recessive mutations in nuclear genes, which encode for respiratory chain subunits or for proteins involved in respiratory chain assembly (81).

In most patients with PDHC deficiency and LS, the enzymatic defect resides in the catalytic E1α subunit of the complex (35). The biochemical defect in cultured lymphoblastoid cells from one patient with LS and PDHC deficiency could be fully corrected by high doses of thiamin pyrophosphate (74), which could have potentially important therapeutic implications.

Complex I deficiency is another important cause of LS. Mutations in the nuclear encoded 23 kD NDUFS8 subunit (62), 18-kD AQDQ (107), NDUFS7 subunit (106), and in the NDUFV1 subunit (88) have been found in patients with LS and complex I defects.

Administration of sodium dichloroacetate (DCA) proved to be beneficial to patients with LS and complex I deficiency, but without known mutations (53). DCA reduces lactate concentration by stimulating the activity of PDHC. DCA also reduces the turnover of subunit E1a of PDHC in cultured fibroblasts (72). These observations suggest that DCA could be one of the most promising compounds for the treatment of mitochondrial encephalopathies not limited to LS.

A more rare molecular defect associated with autosomal recessive LS was identified in two siblings born to

consanguineous parents, who harbored a mutation in the gene coding for the flavoprotein of complex II (succinate dehydrogenase, (13).

Cytochrome c oxidase (COX) deficiency is one of the most common causes of autosomal recessive LS. In a subset of LS patients, COX activity is reduced in all tissues (63). Using microcell-mediated chromosome transfer techniques and linkage analysis, Zhu and colleagues (114) and Tiranti and colleagues (105) were able to map the molecular defect in patients who belonged to a single complementation group. In these individuals, the genetic defect resides in a gene of unclear function, SURF1, on chromosome 9q34. Surf1, similarly to its yeast homologue SHY1 (69), is translocated to mitochondria, where its presequence is cleaved. Mature SURF1 is localized to the inner mitochondrial membrane, where it presumably participates in the assembly of COX (104, 113).

In a different form of LS and COX deficiency, clinically characterized by encephalopathy and severe cardiomyopathy, the gene defect was identified in another COX assembly gene, a human homologue of two related yeast genes, SCO1 and SCO2 (79). It has been proposed that, at least in yeast, the SCO proteins might be copper-binding proteins required for the insertion of copper ions in COX subunit I and II (36).

Nuclear gene mutations affecting mitochondrial proteins

Hereditary spastic paraplegia. Hereditary spastic paraplegia is a progressive disorder resulting in paraparesis with onset in childhood or in early adulthood. Upper motorneurons are selectively involved, but ancillary symptoms, such as ataxia and retinitis, are not uncommon. Autosomal dominant, X-linked, and autosomal recessive modalities of inheritance have been described (41). In families with a recessive form of the disease mapped to chromosome 16q24.3 (30), the disease gene, called paraplegin (SPG7), has been identified and cloned (24). Paraplegin has a high degree of homology with yeast ATP-dependent zinc metalloproteases that are active in mitochondria, and may have a chaperone-like activity (61). Homozygous deletions or frameshift mutations of the paraplegin gene cause OXPHOS dysfunction with COX deficiency and mitochondrial proliferation (i.e. ragged red fibers) in muscle (24), although the underlying pathogenic mechanism is still unclear.

Friedreich's Ataxia. Friedreich's ataxia (FRDA) is the most common of hereditary ataxias. It is clinically defined by the following criteria: autosomal recessive inheritance, onset before age 25, progressive limb and gait ataxia, absent tendon reflexes, signs of axonal sensory neuropathy, and pyramidal signs (40). The FRDA gene has been mapped to chromosome 9q13 (26, 71). In most cases, the genetic alteration is a GAA expansion in the first intron of a gene denominated frataxin (22). Frataxin is differently expressed in tissues, and in the central nervous system it is particularly abundant in the cerebellum and in the spinal cord (22). Homozygous GAA expansion in intron 1, or, more rarely, heterozygous point mutations compounded with heterozygous expansions, cause decreased frataxin expression (21). Frataxin localizes to mitochondria, where the precursor protein is cleaved by mitochondrial peptidases to the mature form (58). A yeast homologue of human frataxin, named YFH1, has been identified (5). Knockout of YFH1 causes intramitochondrial iron accumulation, mitochondrial respiratory defect, and loss of mitochondrial DNA (58). Similarly, in affected human tissues there is an increase in iron (84) and a decrease in the activities of some key mitochondrial enzymes, such as complexes I, II-III, and aconitase (14, 83), all of which contain iron-sulfur groups. MtDNA levels are also decreased in affected tissues. These observations indicate that human frataxin may be involved in mitochondrial iron homeostasis and iron-sulfur clusters synthesis. It has also been suggested that respiratory chain enzyme dysfunction could cause increased oxygen reactive species and further oxidative damage in a self–propagating manner (14).

Wilson's disease. Wilson's disease is an autosomal recessive disease characterized by movement disorders such as dystonia and parkinsonism, psychiatric symptoms, and liver failure, with onset in childhood or adolescence. There is a defect in copper homeostasis, which results in copper accumulation in liver, the basal ganglia of the brain, and kidney. The disease-associated gene encodes for a copper-transport P-type ATPase, called WND (19). The WND protein exists in two isoforms, a 160 kDa, which localizes to the trans-golgi network, and a 140 kDa, which localizes to mitochondria (64). Although the precise functions of the protein is not known, the mitochondrial localization of the 140 kDa WND suggests that this isoform might play a role in the copper-dependent functions of mitochondrial enzymes. Mitochondria in affected tissues have characteristic morphological abnormalities (92), which are also

observed in the mitochondria of Long-Evans cinnamon rats, the animal model of the disease (93). Moreover, increased levels of deleted forms of mtDNA have been identified by PCR amplification in liver from patients with Wilson's disease (68).

Mohr-Tranebjaerg syndrome. Mohr-Tranebjaerg syndrome, or deafness-dystonia syndrome, is an X-linked recessive disorder, characterized by progressive sensorineural deafness, dystonia, cortical blindness, and psychiatric illness. It results from deletions or truncations of a protein, DPP1 (50), homologous to yeast Tim8, a member of the inner mitochondrial membrane transport machinery located in the mitochondrial intermembrane space (55). However, as deletion of Tim8 alone does not affect cell survival in yeast, it remains to be clarified how the loss DPP1 in humans causes mitochondrial dysfunction in the affected tissues.

Other examples of defects in the mitochondrial protein import machinery import have been reported in humans, such as a deficit of HSP60 (a mitochondrial chaperonin) in patients with a severe multisystem disorder and multiple mitochondrial enzyme defect (2, 15).

Mutations of non-mitochondrial proteins

Huntington's disease. Huntington's disease (HD) is a chronic autosomal dominant disease with full penetrance by mid-adult life. The illness is characterized by choreoathetotic movements and by progressive emotional and cognitive disturbances. Selective degeneration of striatal neurons with marked atrophy of caudatum and putamen are the main pathologic correlates. Ultrastructurally, nuclear inclusions have been observed in HD striatum and cortex. HD is caused by an expansion of a CAG repeat in the IT15 gene on chromosome 4, which encodes for a protein of unknown function named huntingtin (1). A defect in energy metabolism has been proposed as one of the potential pathogenic mechanisms underlying HD, based on evidence obtained both in vivo and in post-mortem tissues. Lactate increase has been found by MRI spectroscopy in occipital cortex and basal ganglia of HD patients (49), who also show a reduced Pcr/Pi ratio in muscle (57). Using the respiratory chain complex II inhibitor malonate, Beal and colleagues have produced pathologic lesions in the striatum of experimental animals, that closely resembled those of HD (9). These lesions could be prevented by treating the animals with CoQ10 and nicotinamide (10). Defects of complexes II, III, and aconitase have been described in post-mortem HD brains, particularly in the basal ganglia (17, 38, 99). Further evidence for mitochondrial respiratory chain dysfunction and aconitase defect has been provided by studies of transgenic mouse models of HD (100). These mice also exhibited reduced levels of N-acetylaspartate in brain, as demonstrated by MRI spectroscopy (8). Because N-acetylaspartate is synthesized within mitochondria, its decrease might reflect mitochondrial dysfunction. Transmitochondrial cell lines, generated by repopulating mtDNA-less cells with platelet mtDNA from HD patients, failed to show any respiratory chain defects, suggesting that, at least in platelets, mtDNA does not harbor pathogenic mutations (95).

Despite the increasing evidence in favor of a mitochondrial involvement in the pathogenesis of HD, the mechanisms through which huntingtin with expanded polyglutamine repeats causes mitochondrial dysfunction is not yet well understood.

Amyotrophic lateral sclerosis. Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease affecting the anterior horn cells of the spinal cord and cortical motor neurons. The disease generally starts in the fourth and fifth decade and progresses over an average of three years leading to paralysis and premature death. While the majority of cases are sporadic and due to unknown causes, about 15-20% are familial, and, of these, about 10 % are associated with mutations in the superoxide dismutase 1 gene (82). Because superoxide dismutase 1 (SOD1) reduces the potentially harmful superoxide radical, it has been suggested that familial ALS (FALS) is a consequence of disturbed free radical homeostasis and resulting oxidative stress. It was shown that mouse models carrying these mutations develop severe motor neuron disease (39). As these mutations do not decrease significantly SOD1 activity, a toxic "gain of function" of the mutated protein has been postulated. Among the morphological alterations in motor neurons of mutant SOD1 mice is the presence of massive mitochondrial degeneration. In G93A mutant mice, the loss of muscle strength is immediately preceded by a transient explosive increase in vacuoles derived from degenerating mitochondria in the motor neurons, with little motorneuron death. These mice also exhibited abnormal respiratory chain function (16). These observations suggest that mitochondrial alterations might represent a triggering factor in the onset of the disease (56). Similarly, accumulations of abnormal mitochondrial were observed in anterior horns of patients with sporadic ALS not related to SOD1 mutations (86). Mitochondrial depolarization, an indicator of respiratory chain dys-

function, was observed in neuroblastoma cells transfected with the mutant form of SOD1. These cells also displayed impaired mitochondrial calcium buffering capacity, leading to increased cytoplasmic calcium, a potential stimulus for apoptotic cell death (23).

A mtDNA frameshift mutation in the gene encoding subunit I of COX, was found in one case of sporadic ALS (27). COX deficiency was also identified in skeletal muscle from a series of unrelated sporadic ALS patients (112). A pathophysiological role for mtDNA mutations has been postulated based on biochemical studies of cybrids obtained from mitochondria of sporadic ALS patients, which exhibited abnormal respiratory chain, increased free radical scavenging enzymes, and altered calcium homeostasis (96). Another indication of mitochondrial dysfunction in ALS comes from the observation that supplementation with creatine, which takes part in the mitochondrial energy buffering and transfer system, improves motor performance and extends survival in SOD1 mutant mice (54).

Taken together, these findings strongly suggest that impairment of mitochondrial energy metabolism, possibly caused by mtDNA abnormalities, might play a role in the pathogenesis of ALS.

Progressive supranuclear palsy. Progressive supranuclear palsy (PSP) is a neurological disorder with rapid progression, characterized clinically by cognitive impairment, extrapyramidal symptoms, and palsy of vertical gaze of supranuclear origin. The pathologic hallmark of the disease is the presence in the subcortical regions of the brain of neurofibrillary filaments with diffuse neuronal degeneration and gliosis. Genetic studies have established a significant association between an extended *tau* haplotype (H1) and PSP (6, 28). The neurofilaments that accumulate in PSP contain hyperphosphorylated *tau* (89). There are several pieces of evidence that mitochondrial energy metabolism could be affected in PSP. First, OXPHOS defects have been reported in muscle from PSP (34). Furthermore, in postmortem PSP brains there was a reduction in the activity of α-ketoglutarate dehydrogenase, a key enzyme of the Kreb's cycle, vis-a-vis with normal respiratory chain activities (4). Increased content of malondialdehyde, a marker of lipid peroxidation, was also reported in PSP brains (3). It is conceivable that a combination of mitochondrial dysfunction and oxidative stress could generate a vicious cycle leading to further oxidative damage and neuronal degeneration.

Putative secondary mitochondrial involvement

Parkinson's disease. Parkinson's disease (PD) is a neurodegenerative disorder clinically characterized by bradykinesia, rigidity and tremor. Pathologically, the hallmark of the disease is the loss of dopaminergic neurones in the substantia nigra. The causes of PD are unknown in the majority of cases. A rare familial form has been associated with mutations in the α-synuclein gene (59, 80), although the mechanism by which these mutations cause neuronal degeneration is not known.

Numerous findings have contributed to identifying possible mitochondrial involvement in the pathogenesis of PD. First, it was shown that 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) toxicity, which produces parkinsonism in humans and laboratory animals, is mediated by inhibition of respiratory chain complex I (76). Second, complex I deficiency and oxidative damage were demonstrated in the substantia nigra of PD patients (11, 48, 67, 87), together with reduced immunoreactivity for Complex I subunits (42). Because complex I is the principal source of free radicals in the cell (60), a dysfunctional complex I in the substantia nigra could be responsible for the increased lipid peroxidation and DNA damage (in the form of $OH^{8}dG$) found in PD brains (33). Cybrids containing mtDNA from PD platelets also showed reduced complex I activity (37), strongly suggesting that inherited and/or somatic mtDNA mutations might be responsible for the biochemical phenotype in PD. In rare cases, these mutations might represent the primary cause of the disease, as maternally inherited forms of PD or parkinsonism with complex I deficiency have been reported (90, 97). More frequently, however, mtDNA mutations, either inherited or acquired, could contribute, together with nuclear gene mutations and environmental factors, to the pathogenesis of PD.

Alzheimer's disease. Alzheimer's disease (AD) is the most common form of dementia in the elderly. Approximately 5% of AD cases are inherited with autosomal dominant transmission. These cases are primarily due to mutations in the amyloid precursor protein or presinilin genes. Most patients with AD are sporadic cases without a known genetic defect. The neuropathology of AD patients is characterized by neuronal loss and by the presence of neurofibrillary tangles and amyloid plaques.

Reduced COX activity has been found in AD brains (73) and defects of COX have been identified in AD hippocampus by immunostaining for specific subunits of the complex (12). Reduced immunoreactivity for COX

subunits, more markedly for the mtDNA encoded ones, was also found in AD purkinje cells (77). Similar alterations have been observed in brain following experimental deafferentiation in monkeys (43). COX deficiency has been described in platelets from AD (94). The enzymatic defect could be transferred to cybrid cell lines, suggesting the presence of pathogenic mtDNA mutations (29). However, the mtDNA mutations initially identified in some of those patients were later demonstrated to be only present in nuclear pseudogenes (44, 111). A number of different mtDNA changes have been associated with AD, but none of these studies has been able to conclusively prove the role of mtDNA mutations in the pathogenesis of AD (reviewed by Bonilla and colleagues (12)). Indirect evidence suggesting a potential role of mitochondrial dysfunction in AD comes from the observation of increased oxidative damage in mtDNA from AD brains compared to age-matched controls (70).

Conclusions

A growing body of evidence suggests that impairment of mitochondrial energy metabolism could be involved in the pathogenesis of several neurodegenerative disorders. As reviewed above, some illnesses, such as LS, LHON, and NARP, are caused by specific, primary mtDNA mutations. Others are caused by genetic defects affecting proteins with as yet unknown functions but with clear mitochondrial localization. Mutations in mitochondrial proteins, such as frataxin and paraplegin, cause mitochondrial dysfunction with impaired respiratory chain. The evidence in favor of a mitochondrial role in the pathogenesis of PD, HD, ALS, and AD is more circumstantial. In these cases, mitochondrial dysfunction could be secondary, but still relevant to the development of the disease. It is particularly tempting to hypothesize that an interaction between mitochondrial dysfunction and oxidative damage could trigger a vicious cycle, leading to neuronal degeneration and death.

At this stage, we believe that it is important to develop a better understanding of the role of mitochondrial energy metabolism in neurodegenerative diseases, because it may lead to the development of effective therapeutic strategies, which specifically target mitochondria. These include administration of free radical scavengers, antiapoptotic drugs which acts at the mitochondrial level, or energy buffering compounds, such as creatine.

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