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Authors
Pathak, Divya
Berthet, Amandine
Nakamura, Ken

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Energy Failure: Does It Contribute to Neurodegeneration?

Divya Pathak, PhD[1], **Amandine Berthet, PhD**[1], and **Ken Nakamura, MD, PhD**[1,2]

[1]Gladstone Institute of Neurological Disease, University of California, San Francisco, San Francisco, CA.

[2]Department of Neurology and Graduate Programs in Neuroscience and Biomedical Sciences, University of California, San Francisco, San Francisco, CA.

Abstract

Energy failure from mitochondrial dysfunction is proposed to be a central mechanism leading to neuronal death in a range of neurodegenerative diseases. However, energy failure has never been directly demonstrated in affected neurons in these diseases, nor has it been proved to produce degeneration in disease models. Therefore, despite considerable indirect evidence, it is not known whether energy failure truly occurs in susceptible neurons, and whether this failure is responsible for their death. This limited understanding results primarily from a lack of sensitivity and resolution of available tools and assays and the inherent limitations of in vitro model systems. Major advances in these methodologies and approaches should greatly enhance our understanding of the relationship between energy failure, neuronal dysfunction, and death, and help us to determine whether boosting bioenergetic function would be an effective therapeutic approach. Here we review the current evidence that energy failure occurs in and contributes to neurodegenerative disease, and consider new approaches that may allow us to better address this central issue.

Bioenergetic failure has been suggested to cause neuronal death in a range of neurodegenerative diseases, including Parkinson disease (PD),[1] Alzheimer disease (AD),[2,3] and Huntington disease (HD).[4] However, energy failure has never been directly demonstrated to occur in dying neurons in these diseases or even in intact neurons in genetic models of these diseases. Why, then, is bioenergetic dysfunction considered by many to be a central mechanism that produces neurodegeneration? This assertion is supported by the nearly overwhelming evidence—from human, genetic, and animal studies—that mitochondria are altered in multiple respects in all of these conditions, and because many of these mitochondrial changes have the potential to cause bioenergetic failure. However, whether this actually occurs in affected neurons is almost always unknown. Furthermore, in addition to producing adenosine triphosphate (ATP), mitochondria have other functions, including the production of reactive oxygen species (ROS), calcium buffering, and the regulation of apoptotic pathways, lipid biosynthesis, and neurotransmitter metabolism,[5,6]

Address correspondence to Dr Nakamura, Gladstone Institute of Neurological Disease, 1650 Owens Street, San Francisco, CA 94158. ken.nakamura@gladstone.ucsf.edu.

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and changes in these processes could also contribute to neurodegeneration. Therefore, although suggestive, altered mitochondrial function per se cannot be automatically equated with energy failure.

How, then, can we establish whether bioenergetic dysfunction is a central mechanism that produces neurodegeneration? A major issue is that most of the available tools, techniques, and model systems lack sufficient resolution to establish a direct relationship. The development of new and improved methods that overcome some of these challenges could provide new and important insight into the initial mitochondrial changes that occur in neurodegeneration, and how these affect bioenergetic function.

Before reviewing the evidence for bioenergetic dysfunction in neurodegeneration, we must first define *energy failure*. For the purposes of this review, we define energy failure as insufficient ATP for a cell to maintain its cellular functions and/or defenses against stresses. If relatively mild, energy failure will impair neuronal function–for instance, by blocking synaptic transmission[7]–but may still be compatible with neuronal survival. However, more profound energy failure will trigger active forms of cell death, including apoptosis and/or pathways that involve the release of mitochondrial factors from damaged mitochondria. When particularly severe, there may be insufficient energy for classic apoptotic pathways to proceed, and energy failure may trigger other cell death pathways.[8,9] Energy failure might result either from impaired energy production, increased energy consumption, or both. In addition, energy failure might result from defects in either aerobic or anaerobic respiration, but this review focuses on bioenergetic dysfunction caused by mitochondrial failure.

Evidence for Energy Failure from Mitochondrial Dysfunction in Neurodegenerative Disease

Mitochondrial Changes Identified at Autopsy

The enzymatic function of specific respiratory-chain complexes are decreased in the brain tissue of patients with AD,[10] HD,[11] and PD.[12] With the essential role of these complexes for aerobic respiration, these changes might certainly produce—or at least reflect—bioenergetic stress. However, further mechanistic interpretation is difficult for several reasons. First, many of these changes were assayed from total brain tissue, and likely reflect changes in glia rather than neurons,[13,14] making it impossible to discern whether the same enzymatic changes also occurred in affected neurons. Some studies have specifically targeted individual affected neurons and identified defects in the expression of genes that regulate bioenergetic function.[1,15] However, such changes may still not translate into decreased ATP production,[16] depending on the specific complex inhibited and the extent to which enzymatic activity is compromised. In yet other cases, decreased ATP production might be a compensatory response to decreased ATP demand and, therefore, may not contribute to the degeneration.

A number of other intriguing changes in mitochondrial function have been observed in postmortem tissue, although their effects on bioenergetic function are similarly difficult to predict. For instance, mitochondrial DNA mutations accumulate with age and appear to accumulate at a faster rate in individuals with neurodegenerative diseases,[17,18] although this

is controversial in some cases.[19,20] In many cases, these mutations are found in the affected neuronal subtypes (eg, through laser capture of dopaminergic [DA] neurons[17]). These mutations likely produce respiratory defects, considering that many of the genes encoded by mitochondrial DNA contribute to bioenergetic function, and because the percentage of mitochondrial DNA with deletions is increased in those neurons with decreased cytochrome c oxidase activity,[17,21] although this remains to be formally proved. Alternatively, these mutations might affect other functions, such as ROS production, and/or make little contribution to disease progression.

Other studies revealed intriguing changes in mitochondrial biogenesis. For example, decreased expression of PGC1-α and PGC1-α-regulated genes was observed in DA neurons in patients with PD,[1] in striatal tissue in HD patients,[22] and in the hippocampus of AD patients.[23] Once again, these changes would likely result in bioenergetic dysfunction, but this is also not yet proved.

Nuclear Magnetic Resonance Spectroscopy

Magnetic resonance spectroscopy (MRS) provides one of the only methods to directly visualize energy metabolites in the brains of living patients, and it has provided strong evidence for energy deficits in neurodegenerative disease. For instance, levels of lactate are increased in the basal ganglia and occipital cortex in patients with HD.[24] In addition, MRS studies have revealed decreased resting levels of ATP/(phosphocreatine + inorganic phosphate) in the muscles of symptomatic and presymptomatic HD patients and a decreased maximal rate of ATP production and phosphocreatine recovery after exercise.[25,26] In early HD, ATP levels in the brain also fail to upregulate normally when energy demands are increased.[27] Levels of ATP are also decreased in the midbrain and putamen of patients with early and advanced PD,[28] and levels of high-energy phosphates (ATP and phosphorylated creatine), but not low-energy phosphates (ADP and unphosphorylated creatine), are decreased in the basal ganglia and frontal lobes of patients with progressive supranuclear palsy.[29] MRS approaches, thus, provide strong evidence that energy failure occurs in neurodegeneration. However, at present, they lack the sensitivity to discriminate changes between adjacent neurons and their surrounding glia, and hence are unable to prove that the energy failure occurs within affected neurons, or to provide insight into how any changes may differ in susceptible versus resistant cell types.

Evidence from Mitochondrial Neurotoxins

The susceptibility of vulnerable neurons to inhibitors of the mitochondrial respiratory chain also suggests a role for bioenergetic failure in neurodegenerative disease. For instance, the complex I inhibitors 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and rotenone are selectively toxic to DA neurons,[30,31] and striatal interneurons are selectively susceptible to the complex II inhibitors 3-nitropropionic acid[32,33] and malonate.[34] However, 1 methyl-4-phenylpyridinium (MPP1) may produce death through mechanisms that are at least partly independent of its effects on complex I,[35–37] and even rotenone, a prototypical complex I inhibitor, may exert toxicity through other mechanisms.[36,37] It is thus unclear whether the susceptibility to these toxins truly reflects intrinsic differences in the respiratory chain function between neuronal subtypes, even for those toxins, such as rotenone, that are

imported into all cells equally (in contrast to MPTP, whose metabolite MPP+ is selectively concentrated within DA neurons by the dopamine transporter[38]). Furthermore, even if they do kill susceptible neurons by blocking energy production, this still would not prove that neuronal death actually occurs through bioenergetic failure in the human disease. There is no conclusive evidence that any of these toxins produce the idiopathic conditions, although several epidemiologic studies have associated certain pesticides (such as rotenone and paraquat) with a somewhat higher disease prevalence.[39] Thus, although suggestive, susceptibility of a cell type to a mitochondrial toxin does not directly prove that neuronal death occurs through bioenergetic failure.

Genetic Forms of Neurodegenerative Disease Implicate Mitochondria

The finding that mutations in the mitochondrial protein PINK1 produce an autosomal-recessive form of PD[40] established that specific defects in mitochondria can cause PD. Subsequent studies in *Drosophila*[41,42] and cell-culture models[43,44] linking PINK1 and parkin, another autosomal-recessive PD protein, strongly suggest that mutations in parkin also cause PD through effects on mitochondria. However, the specific mechanism(s) are unclear. A number of functions have been ascribed to PINK1 and parkin, including roles in mitophagy,[43,45] mitochondrial dynamics,[46,47] mitochondrial mobility,[48] and mitochondrial biogenesis.[49] All of these changes might affect mitochondrial bioenergetics (Fig 1), but could also influence other mitochondrial functions. In the case of PINK1, subtle impairments in basal mitochondrial membrane potential and a paradoxical depolarization follow exposure to oligomycin.[50,51] This latter finding has generally been interpreted to arise from reverse transport of protons through the ATP synthase to maintain membrane potential, in the context of a dysfunctional respiratory chain.[51] In agreement with this, a subsequent study using luciferase-based approaches has demonstrated decreased basal ATP levels in the striatum of living PINK1 knockout animals, and an impaired ability of mouse embryonic fibroblasts lacking PINK1 to upregulate ATP synthesis in response to stress.[52] Although these studies still do not establish that ATP levels are actually decreased and limiting within individual neurons or provide insight as to why DA neurons are selectively susceptible, they nonetheless provide some of the strongest evidence to date that mutations in PD proteins produce bioenergetic failure in neurons.

A number of other genes implicated in AD and PD can impact various mitochondrial functions, although it is unknown whether these effects lead to neuronal dysfunction or death. Of particular interest is the relationship between mitochondrial dynamics, the balance between fusion and fission, and bioenergetics. A number of PD-associated proteins, including *α*-synuclein, PINK1, parkin, and LRRK2, as well as amyloid-beta, tau, and huntingtin, disrupt normal dynamics across a range of paradigms. In some cases, normalizing mitochondrial morphology protected against these insults.[46,53–59]

The mechanism by which changes in mitochondrial dynamics might produce degeneration is unknown, but has been hypothesized to ultimately involve bioenergetic failure.[55,60–62] This may occur through changes in the intrinsic function of mitochondria[55,60] and/or changes in the mass or distribution of mitochondria within neuronal processes, for instance, through decreased transit of excessively tubulated mitochondria[61,63] or changes in the rate of

mitochondrial degradation.[58] Understanding the relationship between mitochondrial dynamics and bioenergetics, versus other nonenergetic consequences of altered mitochondrial morphology, will help to clarify how changes in dynamics may contribute to disease.

Mitochondrial DNA Disorders

The neurologic diseases that provide the most compelling evidence for bioenergetic failure are the mitochondrial myopathies. Patients suffering from mitochondrial myopathies show elevated lactate levels,[64] suggesting that these diseases cause impaired aerobic respiration with a compensatory shift toward increased anaerobic respiration. But is this compensation sufficient, or does energy failure still occur? It is somewhat surprising that mice with severely compromised complex I function exhibit broad neurologic and systemic deficits, but fail to show significant changes in ATP or phosphocreatine levels in muscle.[65] In another study, deletion of a mitochondrial transcription factor (Tfam) in skeletal muscle also resulted in only a small decrease in ATP production when standardized to overall muscle mass.[66] However, further analysis revealed a substantial increase in mitochondrial mass, suggesting that dysfunctional mitochondria proliferated to compensate for their impaired bioenergetic function.[66] In yet another study, McKenzie et al showed that mitochondrial mutations producing the syndrome MELAS (mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes) resulted in impaired mitochondrial function. Although ATP levels were largely maintained at baseline through compensation by glycolysis, severe bioenergetic deficits were revealed when glycolysis was blocked.[67] These results thus highlight the importance of assay design to detect mitochondrial failure, and provide evidence that bioenergetic dysfunction can occur with certain mitochondrial mutations. Future experiments will be required to confirm that this energy failure is ultimately responsible for neuronal dysfunction and death.

Contribution of Glucose and Overall Metabolic Changes to Bioenergetic Failure in Neurodegenerative Disease

Although this review focuses on energy failure from mitochondrial dysfunction, primary changes in glucose uptake or metabolism could also produce bioenergetic dysfunction (eg, by impairing glycolysis). Changes in glucose metabolism occur early in the pathogenesis of AD and HD sufferers as well as in those susceptible to these diseases.[68–72] In some cases, this may represent a shift in the extent of glucose allocated to glycolysis versus the pentose–phosphate pathway.[73] However, it is unknown whether changes in glucose metabolism produce energy failure in dying neurons, nor is it clear whether they are the cause or the result of mitochondrial dysfunction in these diseases.

On a broader level, patients and animal models of several neurodegenerative diseases, including AD,[74], HD,[75] and likely PD,[76] exhibit early weight loss that cannot be explained by changes in caloric intake or activity. Although the etiology of this weight loss is unknown, it could reflect underlying changes in mitochondrial and other bioenergetic functions at the cellular level.

Obstacles to Measuring Energy Failure in Neurodegenerative Disease

Considering that bioenergetic failure is a feature common to many neurodegenerative diseases, it is remarkable that our understanding of its role in neurodegeneration is so limited and largely speculative. However, progress in this area has been hampered by a lack of appropriate tools, as well as limitations in the existing approaches and methods.

Model Systems

The limitations of existing model systems greatly impede our understanding of bioenergetics in neurodegeneration. Although neurodegenerative diseases are characterized by the selective vulnerability of specific neuronal populations, many studies rely on cell lines or study neuronal types that are not affected by the disease. This approach can yield important insights. For instance, energy failure might be equally likely to occur in all cell types that express a given protein of interest, and selective degeneration may simply reflect a greater susceptibility to the toxicity of these effects and/or selectively increased expression of the toxic proteins in affected versus unaffected cells. However, in other cases, bioenergetic changes may occur only in certain neuronal subtypes, depending on the presence of discrete characteristics. For instance, susceptible neurons may contain relevant compounds (eg, dopamine) that contribute to mitochondrial impairment, or have mitochondria with subtype-specific functions or properties. Clearly, there are fundamental differences between neurons grown in culture and in vivo, including the extent of myelination,[77,78] axonal arbor size,[79] and oxygen tension,[80,81] that are likely to affect bioenergetic function. We do not know whether the critical mechanisms producing degeneration are recapitulated in culture.

In vivo model systems have similar limitations, and rodent models in particular have consistently failed to replicate important features of the human condition. For PD, no faithful disease-based genetic model has produced the selective loss of DA neurons, with the possible exception of PINK1 knockout loss in rats.[82] This may result partly from the shorter lifespan of mice, but rodent neurons also have intrinsic differences in susceptibility to mitochondrial stressors. For instance, rats are more sensitive than mice to loss of PINK1,[82,83] whereas primates are far more sensitive to the mitochondrial toxin MPTP than mice, which in turn are more susceptible than rats.[84] In this respect, human-derived neurons might provide valuable information, although the lack of in vivo context remains an important limitation.

Subcellular Compartment

Synaptic terminals degenerate early in a range of neurodegenerative diseases associated with impaired energy metabolism, including AD,[85] HD,[86] and PD,[87,88] and in animal models of these diseases,[30] indicating that there may be significant changes in bioenergetic function that are either restricted to—or occur first in—neuronal processes. The regulation and maintenance of energy metabolism in axons versus the cell body almost certainly differ in multiple ways, including the reliance on oligodendrocytes to support the energy requirements of myelinated axons.[78] In axons, loss of myelin results in increased mitochondrial content as well as mitochondrial redistribution,[89,90] and unmyelinated axons may be more susceptible to energy failure.[91] In contrast to the cell body, many synaptic

boutons also lack mitochondria (for instance, only about ½ of hippocampal boutons contain mitochondria[92]), raising questions about how energy is dispersed at nerve terminals as a function of their presence or absence, and whether there are regional gradients of ATP in synapses that may impact neuronal function and/or axonal health (Fig 2). It will be interesting to learn whether regional energy failure can be influenced by changes in the regional distribution or function of mitochondria.

However, despite these important differences, for technical reasons, most studies in intact neurons have focused on the cell body rather than processes. It is unknown whether the bioenergetic status at the cell body provides an accurate reflection of the energy status at the nerve terminal, but there are several reasons why this may not be the case. First, the mitochondria in these compartments may be different, despite coexisting within the same cell. Mitochondrial heterogeneity within the same cell occurs even in nonpolarized cells,[93] the mitochondria in axons are generally much smaller and may be more mobile,[94] and their ability to produce ATP is possibly more susceptible to complex I inhibition.[95] Axonal mitochondria may also be much older, on average, than somatic mitochondria, although very little is known about mitochondrial turnover in neuronal processes. In addition to intrinsic function and mitochondrial mass, regional bioenergetics are also likely to depend on how mitochondria are distributed[92] (see Fig 2). Factors that affect mitochondrial distribution, such as the machinery that moves mitochondria and mitochondrial shape—which is, in turn, regulated by mitochondrial dynamics—are likely to affect bioenergetic function to a far greater extent in the axon versus the cell body (see Fig 2). Differences in local energy requirements, such as the energy requirements for synaptic transmission in neuronal processes, are also likely to differentially impact bioenergetic function at the nerve terminal versus the cell body. It is thus likely that the bioenergetic status is quite different between the cell body and processes, suggesting the need to directly examine bioenergetic function in axons and dendrites.

Tools to Measure Bioenergetic Function Specifically in Neurons

Our ability to study bioenergetic function specifically in neurons is limited by a lack of appropriate tools. At present, there are a number of important approaches to study bioenergetic function in brain tissue as a whole, such as: (1) measurements of regional brain activity and metabolism by positron emission tomography and functional magnetic resonance imaging[72,73,96]; (2) measurements of key energy metabolites, including lactate, creatine, phosphocreatine, and ATP, by MRS[27,64,97]; or by (3) high-performance liquid chromatography after microwave fixation of animal tissues.[98] These approaches have provided clear evidence for bioenergetic changes in specific brain regions, forming much of the rationale for ongoing studies in the area. However, they generally lack cell-type specificity and thus cannot provide conclusive evidence for energy failure within specific neuronal populations and their subcompartments. In certain cases, some cell-type specificity has been attained by combining MRS and measurements of energy metabolites with transgenic approaches targeting specific glial cell types,[78,99] and it may be possible to apply similar methods to study neurons.

There is a growing number of methods to assay bioenergetic function within cultured neurons. Among these approaches, new technical advances allow for the sensitive analysis of respiration, glycolysis, and other metabolic functions in adherent cells, including cultured neuron–based models of neurodegenerative disease.[100,101] In addition, assays with radiolabeled glucose can monitor bioenergetic flux through glycolysis and the tricarboxylic acid cycle.[102,103]

Of particular importance, however, may be new tools that allow measurements within individual neurons, thus factoring out the oftentimes underestimated contribution of glia and allowing the study of specific neuronal subpopulations and subcompartments, such as the nerve terminal (Fig 3). There are now arrays of fluorescence-based sensors that measure bioenergetic function, including those targeting ATP[104–106] and glucose.[107,108] Although there is no way to directly assay respiration at a subcellular level in mammalian neurons, approaches have been developed to allow for measurements of energy production on a single-neuron level.[109,110] These methods complement longstanding approaches, such as the measurement of mitochondrial membrane potential ($\Phi\Psi_m$) with voltage sensitive dyes,[111,112] and the use of synaptosomes to study the respiratory function of isolated synaptic boutons.[16,113] Thus, these provide new opportunities to understand whether and how energy failure contributes to neuronal dysfunction and death. Although these single-cell approaches are applied primarily to in vitro cell-culture paradigms (see Fig 3), future in vivo applications with 2-photon–based approaches have tremendous potential.

Assay Design to Target Mitochondrial Bioenergetics

Optimizing assay sensitivity is likely critical for models of neurodegenerative disease where the phenotypes may be subtle, given that these diseases can take years to develop in humans. It may be necessary to perform assays under conditions that minimize alternative energy sources (namely glycolysis) and thus force reliance on mitochondria for energy. For instance, cell lines are commonly grown in the presence of galactose, which is primarily metabolized through the pentose–phosphate pathway, thus forcing reliance on oxidative phosphorylation for ATP.[114,115] In this way, the effects of mitochondrial dysfunction or loss on ATP levels and survival can be revealed.[45,105] However, galactose is rarely used in studies of neurodegeneration in primary neurons, and glucose levels in standard neuronal culture and imaging buffers are roughly 20-fold higher than in rat brain (1–1.5 mM[116,117]). Under these nonphysiological conditions, glycolysis compensates for deficits in aerobic respiration, allowing cells to maintain nearly normal levels of ATP and support key functions including synaptic transmission,[105,118,119] and this markedly decreases the sensitivity to observe and detect mitochondrial dysfunction.[67]

Conclusions and Directions

Considering the many unknowns about whether and how energy failure contributes to neurodegeneration, it is not surprising that most clinical trials targeting bioenergetics have had little success. In some cases, the limited success may have resulted from limitations in study design or execution, and hopefully ongoing studies will have better results. Importantly, the conditions where restoring bioenergetics has been most successful, such as

replenishing CoQ10 in some individuals with primary CoQ10 deficiency[120,121] or creatine in guanidinoacetate methyltransferase deficiency,[122,123] are diseases where we have significant insights into the defective element and how to replace it. Clearly, we require a far deeper understanding of how mitochondrial changes lead to energy failure. Understanding these mechanisms will require that we disentangle the effects of mitochondrial morphology, transport, turnover, and ROS formation on bioenergetic function. In addition, in many cases, energy failure may not be an initiating insult, but may occur downstream within cell-death pathways. In those instances, we must understand whether modulating energy failure is still potentially useful as a therapeutic intervention, or whether the affected cells are past the point of no return. Understanding how, when, and in which cells or subcellular compartments energy failure occurs, as well as the threshold levels required to produce neuronal dysfunction and death, would greatly clarify the therapeutic potential of bioenergetic restoration for neurodegenerative disease.

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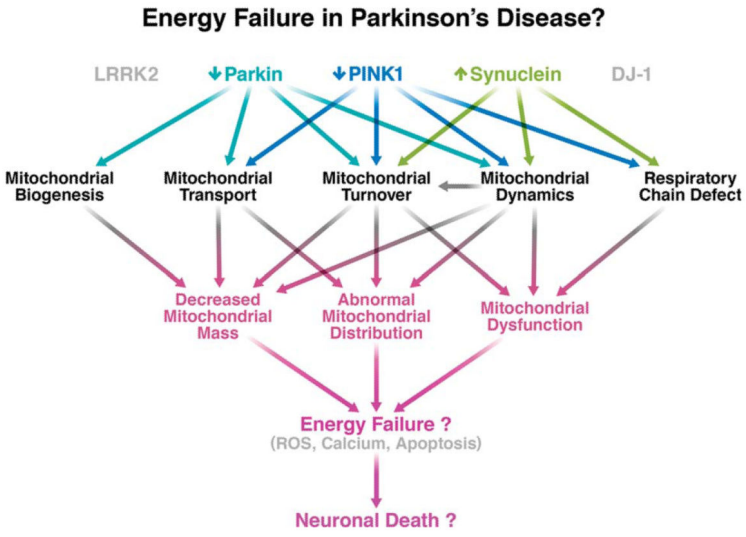


FIGURE 1.

Potential mitochondria-based mechanisms by which Parkinson disease proteins may produce energy failure and neuronal death. The schematic illustrates the known effects of loss of parkin or PINK1 (mitochondrial biogenesis,[49] mitochondrial transport,[48] mitochondrial turnover,[44,45] dynamics,[46,58] and respiration[50,51,124]) or increased synuclein (mitochondrial turnover,[125] dynamics,[54,55] and respiration[126,127]). These primary changes may result in disruptions of the normal mitochondrial distribution and/or function, and this in turn could lead to energy failure and neuronal death. Other mitochondrial functions, such as reactive oxygen species (ROS) production, calcium buffering, and roles in apoptotic pathways could also be altered and contribute to cell-death pathways. DJ-1 and LRRK2 can also affect mitochondrial function,[128–130] but are not depicted in this schematic.

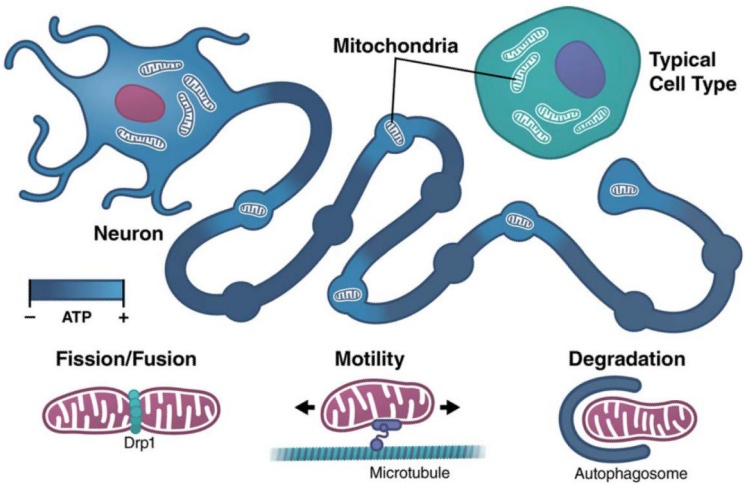
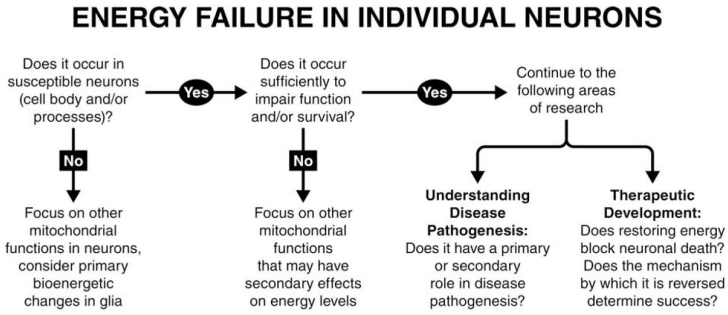


FIGURE 2.

Regulation of mitochondrial bioenergetics in axons. In most non-neural cells, the capacity of mitochondria to produce energy depends on the mitochondrial mass and function, but they may be less dependent on subcellular distribution due to adenosine triphosphate (ATP) diffusion. In axons, however, a normal distribution of mitochondria may also be required to minimize energy gradients. This is illustrated here by the hypothetical gradations in color in the neuron, in which lighter blue reflects higher ATP levels, whereas darker reflects lower levels. Therefore, factors that disrupt the normal distribution of mitochondria, such as mitochondrial dynamics (the balance between mitochondrial fusion and fission) and mitochondrial motility may have more prominent effects on energy levels in axons. Notably, mitochondria in axons are also smaller and more mobile[94] and may have different lifespans than those in the cell body, suggesting that the intrinsic function of mitochondria in the cell body versus axons may also differ.



Tools to Study Mitochondrial Bioenergetics in Individual Intact Neurons and Their Subcompartments

Model Type	Method	Current Standing
Cultured neuron from rodent/human	Mitochondrial membrane potential, ATP/energy metabolites	Technology and/or methods partly available
	Respiration	Requires new methods
In vivo model systems	Mitochondrial membrane potential, ATP/energy metabolites	Technology and/or methods developing (likely to be feasible soon)
	Respiration	Requires new methods
Human disease	Mitochondrial membrane potential, ATP/energy metabolites, oxygen consumption	Requires new methods

FIGURE 3.

Energy failure in individual neurons. The schematic illustrates an algorithm of critical but challenging questions to determine whether energy failure occurs in individual neurons, including their processes, whether and how it contributes to degeneration, and how it might be targeted therapeutically. The table summarizes the availability of tools and methods to assess the bioenergetic function of mitochondria in individual neurons in model systems and human disease. ATP = adenosine triphosphate.