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Forum Editorial

CNS Mitochondria in Neurodegenerative Disorders

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In the past 10 years, our view of CNS mitochondria has changed from that of the necessary, but often ignored, producer of cellular energy to that of a central player in the etiology of neurodegeneration. Articles in this issue highlight some of the multiple ways that CNS mitochondria contribute to both neurodegeneration and maintenance of neural homeostasis. Mitochondrial enzymatic defects, DNA mutations, permeability transition, release of signaling proteins, and production of reactive oxygen species (ROS) have each, in turn, been heralded as causal in various neurodegenerative mechanisms. Energetic deficits can result from all of these mechanisms. Genetically compromised mitochondria, whether from inborn errors of metabolism or mitochondrial DNA (mtDNA) mutations, appear to affect the CNS more readily than other tissues, suggesting that the brain is selectively vulnerable to metabolic defects (22). Chronic compromise of specific mitochondrial enzymes results in regionally selective neuronal loss (2, 20). Calcium and oxidative overload can trigger the permeability transition and mitochondrial demise (7). Additionally, acute or environmentally triggered injuries may result in production of toxic ROS by several key mitochondrial enzymes, as addressed from two complementary points of view by Zeevalk *et al.* (33) and Adam-Vizi (1) in articles in this issue. In an organ with extremely limited energy stores, mitochondrial compromise of any sort engenders functional consequences and eventually CNS pathology.

Beyond simply being implicated in a single pathway toward cell death, mitochondria appear responsible for discrete early steps of both necrosis and apoptosis. In response to excitotoxic stimuli, mitochondrial calcium overloading may trigger depolarization, swelling, and loss of small solutes, known as a mitochondrial permeability transition (mPT) (7, 8). The mPT has become a popular degenerative mechanism, often invoked when mitochondria are compromised. In the CNS, the mPT appears to be involved in acute neurodegeneration associated with excitotoxic stimuli (9). Cytochrome *c* (Cyt *c*) release remains the identifying signature of mitochondrial involvement in early apoptotic signaling, but this does not imply a mPT has occurred (14). mPT activation has been invoked in apoptotic cascades, although without functional mitochondria to produce sufficient ATP, completing apoptosis would appear difficult (32). BAX channels or other outer mitochondrial membrane protein channels may be responsible for Cyt *c* release associated with apoptotic signal cascades. Mitochondria also act as an intersection point for both necrosis and apoptosis. The availability of mitochondrially generated ATP may determine which way a neuron chooses to die (19). Cyt *c* may be released when the permeability transition ruptures outer mitochondrial membranes. A permeability transition may also occur when Cyt *c* acts on the endoplasmic reticulum to release Ca^{2+} to neighboring mitochondria (4). Such a signal might occur very late in the execution phase of apoptosis at a time appropriate for programmed cell dismantling. Thus, mitochondria may become involved recurrently in cell death processes through intersecting, looped, or positive feedback pathways, as reviewed by Jemmerson *et al.* (14).

ROS production can harm both mitochondria and the neurons in which they are created. ROS may be generated by multiple enzymes within the electron transport chain and other metabolic pathways, as Adam-Vizi reminds us (1). For the electron transport chain, low levels of ROS are a by-product, representing systemic inefficiencies (24). Inhibition of one mitochondrial enzyme can produce oxidative stress and ROS, and ROS in turn can inhibit additional mitochondrial processes, as pointed out by Zeevalk *et al.* (33). In an organelle specialized to detoxify molecular oxygen, a careful balance must be maintained during normal operation to minimize the risk of such recurrent ROS injury (24, 33). Thus, neurons must also possess abundant neuroprotective strategies.

Mitochondria contain abundant superoxide dismutase and glutathione as first responders against the ROS generated by the electron transport chain. Neuronal survival depends critically upon these, as shown by the increased susceptibility of the manganese superoxide dismutase knockout mouse to ischemia (16). But subtler protective strategies also exist, as demonstrated in several research articles in this issue (17, 21, 25). Endogenous mitochondrial uncoupling proteins, now recognized throughout the CNS, lower ROS production and Ca^{2+}

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accumulation by depolarizing mitochondria, described by Kim-Han and Dugan (17). Endogenous melatonin, which gives the substantia nigra its name, may be there specifically to prevent neuronal demise arising from the oxidative potential of high concentrations of monoamines and a predisposition to complex I inhibition, reported by Sousa and Castilho (25). Perez-Pinzon *et al.* explain how a mild increase in mitochondrially produced ROS associated with a short ischemic event may activate redox-sensitive protein kinase signaling cascades responsible for neuroprotective ischemic preconditioning (21). Additionally, mitochondria may change their sensitivity to calcium in response to disease progression. In early stages in a mild mouse model of Huntington's disease, striatal mitochondria become more resistant to calcium induction of the permeability transition, demonstrating a compensatory plasticity to the stresses of the genetic defect (5).

Enzymatic detoxification of ROS is just one way that mitochondria promote organellar and cellular survival. With so great a focus on the involvement of mitochondria in cell death pathways, the multiple beneficial roles of this organelle are often neglected. Beyond ATP generation and neurotransmitter metabolism, mitochondria are responsible for fixation of oxygen (24), a significant detoxification process preventing oxidation of many other cellular constituents. Mitochondria act as a redox buffer, helping to maintain the oxidation status of appropriate cellular constituents, and mitochondrial peroxidases and monooxygenases detoxify xenobiotics, although these are not well studied in the CNS (3, 12, 23). And on a very regular basis, neuronal mitochondria act as an important temporary sink for the physiological elevations of cytosolic Ca^{2+} that occur with every action potential (31).

Novel mitochondrial functions may be more intimately woven into the fabric of cellular livelihood and survival than previously thought, as addressed in several articles in this issue (15, 21, 29). Mitochondria may influence cytosolic properties such as axonal transport, as reported by Trimmer and Borland (29). Cellular signal transduction pathways normally associated with plasticity may be regularly activated after low-level mitochondrial ROS generation producing neuroprotection, as reviewed by Perez-Pinzon *et al.* (21). Jonas *et al.* demonstrate that proteins associated with apoptotic signaling may play an entirely different role during normal neurotransmission (15).

Do CNS mitochondria participate in cell death pathways to a greater extent than mitochondria from other tissues? This is hard to say. The balance between cellular life and death in nonregenerating neurons is more precarious than in cell types that possess greater regenerative capacity. Energy supplies are limited in the CNS, so continual ATP production by mitochondria becomes critically important. The decision of a neuron to commit suicide or succumb to injury will have a greater negative impact on brain circuitry as pathways are pruned and redundancies eliminated. Certainly, a growing number of neurodegenerative diseases claim a mitochondrial deficiency of one sort or another. Friedreich's ataxia results from improper handling of mitochondrial iron by the protein frataxin (6). Parkinson's disease may involve inhibition of complex I of the electron transport chain, oxidative damage, and, in some cases, a defect in the putative mitochondrial protein kinase, PINK1 (11). Specific mutations in mtDNA produce retinopathy in Leber's hereditary optic neuropathy and mental retardation in MELAS (mitochondrial encephalopathy with lactic acidosis and stroke) and have been implicated in Alzheimer's disease (18, 30). Inhibition of complex II of electron transport mimics the pathophysiology of Huntington's disease (20). Deafferentation results in mPTs and necrotic death of hair cells (13). Spinal cord injury and traumatic brain injury both create acute excitotoxic lesions involving permeability transitions (27). Ischemia and reperfusion produce core and penumbral lesions with elements of apoptosis, necrosis, and mitochondrial involvement (9). ROS production from easily oxidized monoamines, mitochondria, or Fenton reactions has been implicated in Parkinsonís disease, Alzheimer's disease, and amyotrophic lateral sclerosis, as well as ischemia–reperfusion injury (33). This growing list of neurodegenerative conditions linked to mitochondrial malfunction attests to the multiple, central roles of this important organelle.

Are mitochondria to be forever cast as the villain in every tragic neurodegenerative ending? Arguably, in each case, the neurodegeneration results from an abnormality that affects a mitochondrial process. With the exception of mutations in mtDNA, mitochondria do not initiate cell death. They can be viewed as part of a homeostatic "thermostat" determining if neuronal disruption is sufficient to warrant suicide. As an organelle and evolutionarily adopted symbiant (10), mitochondria have become integrated into the normal functioning of cellular and, hence, neuronal life. What has become clear is that this symbiosis extends beyond that of mutual survival. Mitochondria have also become essential partners in signaling and implementing cell death. At the cellular level, some biochemical processes protect cells from external insults and loss of homeostasis, and others promote cellular demise in the face of insurmountable insults and internal disorder. At the mitochondrial level, mechanisms promoting and signaling mitochondrial survival or suicide remain largely unexplored. How these processes will interact with those of the host neuron remains open for exploration. The mechanisms of mitochondrial fission and fusion appear to influence cell death pathways (26, 28). Whether or not altered regulation of mitochondrial biogenesis or degradation might contribute to the etiology of neurodegenerative diseases awaits further experimentation.

ABBREVIATIONS

Cyt *c*, cytochrome *c*; mPT, mitochondrial permeability transition; mtDNA, mitochondrial DNA; ROS, reactive oxygen species.

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