UPDATE ARTICLE

Mitochondria and the central nervous system: searching for a pathophysiological basis of psychiatric disorders

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Introduction: Mitochondrial dysfunction has been postulated to participate in the development of many neuropsychiatric disorders, but there is no consensus as to its role. The aim of this paper is to review recent studies and to outline the current understanding of the association between mitochondrial dysfunction and psychiatric disorders.

Methodology: We reviewed articles that evaluated mitochondrial dysfunction and psychiatric disorders, with a particular focus on depression, bipolar disorder, anxiety disorders, obsessive-compulsive disorder, and autism spectrum disorder, and the association between mitochondrial dysfunction and development of these disorders.

Results: Evidence suggests that alterations in mitochondrial morphology, brain energy metabolism, and mitochondrial enzyme activity may be involved in the pathophysiology of different neuropsychiatric disorders, given their key role in energy metabolism in the cell.

Conclusions: Understanding the interactions between mitochondrial dysfunction and development of psychiatric disorders may help establish more effective therapeutic strategies for these disorders and thus lead to better outcomes for affected subjects.

Keywords: Mitochondria; central nervous system; neuroplasticity; cell death

Introduction

Biological systems cannot be described as random molecules commanded by physical and chemical laws of diffusion and casual interactions. It is essential to understand biological phenomena as part of a large system; thus, the cell is now understood as an assembly of molecular machines made of proteins that interact to preserve their functions. The same occurs with the structure and function of mitochondria, and the traditional belief that mitochondria are autonomous organelles is changing. The current challenge is to understand the structural and functional cooperation of mitochondria with the rest of the cell, their relation to the endoplasmic reticulum, and the cross-talk between nuclear and mitochondrial genetic machinery.

Mitochondria are essential for the life of the cell. They produce most of the adenosine triphosphate (ATP) by oxidative phosphorylation. Mitochondria have two membranes (outer and inner), an intermembrane space, and an internal matrix. The inner mitochondrial membrane contains the electron transport chain (ETC), the molecular machinery for energy production. Five protein complexes form the ETC. Of these, three (I, III, and IV) pump protons (H+) through the inner membrane, generating a H+ gradient required for the synthesis of ATP at complex V (ATP synthase). The mitochondrial genome codes for 13 of the ETC proteins. The cell nucleus encodes other mitochondrial proteins (more than 1,000), which mediate processes such as the regulation of ion homeostasis, stress responses, cell survival, and signal transduction.

Neuronal energy supplies are completely dependent on mitochondrial oxidative phosphorylation. Neurons have limited capacity to obtain energy through glycolysis when oxidative phosphorylation is compromised, which makes them particularly vulnerable to mitochondrial dysfunction.

The aim of this paper is to review recent findings and outline the current understanding of the association between mitochondrial dysfunction and psychiatric disorders, with a particular focus on depression, bipolar disorder (BD), anxiety disorders, obsessive-compulsive disorder, and autism spectrum disorders.

More than a power station

It is generally assumed that the mitochondrion is the energy-providing organelle of the cell, but it processes several other compounds as well. Neurotransmitters and neurotrophic factors control mitochondrial dynamics.
through their influence upon neuronal energy metabolism, Ca$^{2+}$ homeostasis, and dendritic and axonal motility.\textsuperscript{5}

Many investigations have focused on the role of mitochondria in neurogenesis, especially during neuronal differentiation. The amount of this organelle per cell increases, while the velocity at which mitochondria move decreases, as neurite outgrowth slows and synaptogenesis takes place.\textsuperscript{9} A study by Vayssière et al.\textsuperscript{9} showed that treatment with chloramphenicol (an inhibitor of mitochondrial protein synthesis) prevents cell differentiation, whereas oligomycin (an inhibitor of the mitochondrial ATP synthase) does not, suggesting that increased mitochondrial mass (but not ATP production) is required for neuronal differentiation. Additionally, the focal application of nerve growth factor (NGF) to growing axons results in an accumulation of mitochondria near the site of NGF stimulation by a mechanism that involves docking interactions with the actin cytoskeleton, suggesting a role for mitochondria in facilitating growth cone responses to neurotrophic factors.\textsuperscript{10}

Presynaptic terminals characteristically contain multiple mitochondria, because the majority of the ATP produced is required to maintain synaptic ion homeostasis and phosphorylation reactions.\textsuperscript{5} Looking beyond the obvious function of this organelle, recent findings from experimental models in which the motility and function of mitochondria were visualized suggest that mitochondria play active roles in synaptic plasticity.\textsuperscript{5}

Interestingly, the movement of mitochondria into dendritic protrusions during synaptogenesis correlates with the development and morphological plasticity of spines; when dendritic mitochondrial content is increased, the number and plasticity of spines and synapses enhances greatly.\textsuperscript{11} It remains to be determined if and how recruitment of mitochondria within active synapses contributes to long-term changes in synaptic strength.\textsuperscript{5} Besides, it is known that changes in mitochondrial functions, such as Ca$^{2+}$ regulation, energy metabolism, and oxyradical production, play a role in synaptic plasticity as well.\textsuperscript{5}

**Mitochondria: the crucial signaling**

Studies have showed emerging roles of mitochondria in neuroplasticity.\textsuperscript{11-13} Several prominent signaling pathways that stimulate mitochondrial biogenesis and energy metabolism, while simultaneously regulating neuroplasticity, have been demonstrated.\textsuperscript{13} Mitochondria are distributed throughout the length of axons and presynaptic terminals. In addition, they are found in dendrite shafts and associated with dendritic spines.\textsuperscript{14,15} Mitochondria also participate in the metabolism of reactive oxygen species (ROS), calcium signaling and apoptosis.\textsuperscript{5}

Among many specialized cell types in the body, neurons are particularly remarkable. They have tree-like shapes, are electrically excitable, and act in signal detection, integration, and storage, as well as in the generation of adaptive responses.\textsuperscript{12} Through the use of imaging and molecular biology techniques for the study of mitochondria, several surprising properties and functions of mitochondria in neuroplasticity have been revealed. Mitochondria move rapidly within and between subcellular compartments\textsuperscript{16}; undergo fission and fusion\textsuperscript{17}; respond (e.g., move, change their energy output, take up or release calcium) to electrical activity and activation of neurotransmitters and growth factor receptors\textsuperscript{18}; and function as signaling outposts that contain kinases, deacetylases, and other signal transduction enzymes.\textsuperscript{19}

Indeed, events in learning and memory processes, such as long-term potentiation (LTP), have been associated with changes in mitochondria.\textsuperscript{20-22} Other studies suggest that mitochondria work as mediators of some of the effects of glutamate and brain-derived neurotrophic factor (BDNF) on synaptic plasticity. BDNF is known to promote synaptic plasticity, partly because it enhances mitochondrial energy production\textsuperscript{23} and increases mitochondrial respiratory coupling at complex I.\textsuperscript{24} Furthermore, BDNF expression and signaling is increased in response to environmental factors – such as exercise and cognitive stimulation – that increase cellular energy demand.\textsuperscript{25}

Although changes in the location of mitochondria within axons and dendrites may play roles in synaptic plasticity, rapid functional changes in mitochondria are increasingly being implicated in synaptic plasticity. These changes may include mitochondrial Ca$^{2+}$ uptake or release, production of superoxide and other ROS, and release of proteins and other factors.\textsuperscript{13}

**Apoptosis**

Apoptosis is the prototypical form of programmed cell death (PCD) in neurons during development and adult cell turnover, and it may also occur in a range of neurodegenerative conditions. Under normal circumstances, apoptosis is suppressed, as a result of the rigorous compartmentalization of catabolic enzymes and their activators. Morphologically, it is characterized by cell shrinking, membrane blebbing, and karyorrhexis.\textsuperscript{5} Mitochondria are also involved in cell death, being essential in many apoptotic responses. On a biochemical level, two apoptotic cascades that result in the activation of the executioner caspases 3 and 7 can be distinguished: an intrinsic pathway in which mitochondria play a pivotal role, and an extrinsic pathway that bypasses mitochondria.\textsuperscript{26} In the extrinsic pathway, the engagement of a death receptor such as cluster of differentiation 95 (CD95) by its ligand recruits Fas-associated death domain protein (FADD), which in turn recruits caspase-8. The close proximity of the inactive caspase-8 monomers forces their dimerization, triggering catalytic activity and self-cleavage, which further stabilizes caspase-8 in its active form. Upon release into the cytosol, caspase-8 can either cleave and activate effector caspases, or cleave BH3 interacting-domain death agonist (BID), which induces mitochondrial outer membrane permeabilization. The subsequent activation of caspase-8 initiates the caspase cascade to activate downstream effector caspases, involving caspases -3, -6, and -7, leading to
apoptosis of the cell.\textsuperscript{27} The intrinsic pathway, which predominates in neurons, is triggered by signals as trophic factor withdrawal, moderate overactivation of glutamate receptors, oxidative stress, and DNA damage.\textsuperscript{8} These triggers activate kinases and transcription factors that induce mitochondrial translocation of Bax and Bak, which form pores in the outer mitochondrial membrane.\textsuperscript{5}

Mitochondria also participate in death-regulating biochemical signals. For example, cytochrome c is restricted to the mitochondrial intermembrane space, which prevents its interaction with apoptotic-protease-activating factor 1 (Apaf-1), a cytosolic protein. When this membrane is compromised, cytochrome c binds to Apaf-1, leading to allosteric activation of pro-caspase-9, which in turn activates caspase-3.\textsuperscript{28} In the same way, Smac/DIABLO and Omi/HtrA2, two intermembrane proteins, are usually separated from cytosolic inhibitors of apoptosis proteins (IAPs). Once mitochondrial membrane permeabilization (MMP) occurs, Smac/DIABLO and Omi/HtrA2 inactivate IAP, preventing caspase -3 and -9 inhibition. Two DNAases, apoptosis inducer factor (AIF) and endonuclease G, are also normally confined to the mitochondrial intermembrane space, but following MMP they can move to the nucleus and mediate chromatinolysis.\textsuperscript{29}

MMP is a key event in physiological as well as pathological cell death\textsuperscript{30} and it is regulated at multiple levels. Many proapoptotic agents can induce MMP, including Ca\textsuperscript{2+}, ROS, lipid messengers (e.g., ceramide and ganglioside GD3), and stress kinases. Briefly, MMP formation is facilitated by proapoptotic proteins from the Bcl-2 family, and is inhibited by antiapoptotic Bcl-2-like proteins.\textsuperscript{30}

In this regard, several studies have sought to understand the role of each of the proteins involved in the process. While caspase inhibition can prevent cell death, it does not prevent cytochrome c release, compromising mitochondrial ATP generation and increasing superoxide production. These alterations can make neurons vulnerable to necrosis.\textsuperscript{5} This is similar to AIF and HtrA2, which could impair mitochondrial function when released into the cytosol.\textsuperscript{31,32} In addition, studies have shown that mitochondria can themselves release controlled amounts of cytochrome c, Smac, HtrA2, and AIF, by a still-unclear mechanism.\textsuperscript{33,34} Inhibitors of caspase -1 and -3 modify LTP of synaptic transmission in hippocampal synapses,\textsuperscript{35,36} indicating functions for apoptotic cascades in synaptic plasticity.

**Reactive oxygen species**

Mitochondria are the main intracellular source of ROS\textsuperscript{5,37}. ROS production contributes to mitochondrial damage in a range of pathologies and is also important in redox signaling from the organelle to the cell.\textsuperscript{38,39}

Each complex of the mitochondrial respiratory chain has a singular function and works in association with the others. A fault at any part of the chain can disturb energy supply. In the absence of ADP, the movement of H\textsuperscript{+} through ATP synthase ceases and electron flow slows down, decreasing the speed of the respiratory chain (State IV respiration), and O\textsubscript{2}− formation increases.\textsuperscript{40} In Complex I, the primary source of O\textsubscript{2}− appears to be one of the iron-sulfur clusters.\textsuperscript{41-43} In Complex III, most of the O\textsubscript{2}− appears to be formed as a result of the autodissociation of ubisemiquinone.\textsuperscript{44,45} In addition, O\textsubscript{2}− interacts with nitric oxide to generate peroxynitrite. Peroxynitrite nitration of tyrosine residues impairs the formation of monoaminergic neurotransmitters and other aminergic compounds.\textsuperscript{46}

On the other hand, the mitochrondron possesses various antioxidant defenses that detoxify O\textsubscript{2}− and H\textsubscript{2}O\textsubscript{2}. Superoxide is enzymatically converted to H\textsubscript{2}O\textsubscript{2} by a family of metalloenzymes called superoxide dismutases (SOD).\textsuperscript{47} H\textsubscript{2}O\textsubscript{2} can diffuse to the cytosol and then be converted to H\textsubscript{2}O by glutathione peroxidase and catalase. Moreover, mitochondria use several antioxidant molecules, such as coenzyme Q10 (ubiquinone), creatine, nicotinamide, and glutathione, to interrupt or minimize oxidative processes.\textsuperscript{5}

Despite their potential to cause damage, ROS act on signaling functions in physiological processes, including synaptic plasticity and learning and memory.\textsuperscript{48}

**Ca\textsuperscript{2+} signaling**

Mitochondria also play a role in calcium homeostasis.\textsuperscript{18,49} Calcium (Ca\textsuperscript{2+}) is the principal second messenger that contributes to the regulation of both neurotransmission and short- and long-term neuronal plasticity in the brain. The role of Ca\textsuperscript{2+} signals in apoptosis has been further reinforced by the demonstration that antiapoptotic proteins (such as Bcl-2) decrease Ca\textsuperscript{2+} levels in the endoplasmic reticulum (ER) and reduce cytosolic and mitochondrial Ca\textsuperscript{2+} responses to extracellular stimuli by increasing the leak of Ca\textsuperscript{2+} from the ER.\textsuperscript{50-53} Proapoptotic proteins, on the other hand, exert the opposite effect.\textsuperscript{54}

The fine spatial and temporal organization of intracellular calcium signals is essential to central nervous system (CNS) function.\textsuperscript{55} Signals are conveyed throughout the CNS by local changes in calcium concentration ([Ca\textsuperscript{2+}]c).\textsuperscript{55} Thus, the Ca\textsuperscript{2+} signals that are essential for synaptic transmission and therefore for transmission of information throughout the CNS are transmitted to the mitochondria, where it is assumed that Ca\textsuperscript{2+} modulates mitochondrial metabolism as described elsewhere – with upregulation of the TCA cycle, ATP synthase, and the aspartate carrier,\textsuperscript{56} and presumably with a consequent increase in the supply of ATP.

Alternatively, local changes in intracellular Ca\textsuperscript{2+} concentration ([Ca\textsuperscript{2+}]c) can diffuse across the cell, leading to an effect at a distant site. Indeed, mitochondrial Ca\textsuperscript{2+} overload has long been associated with necrosis in heart ischemia-reperfusion injury and excitotoxicity.\textsuperscript{57}

An important element of the neuronal signaling machinery is the expression of glutamate receptors. Among them, two are Ca\textsuperscript{2+} permeable: the N-methyl-D-aspartate (NMDA) receptor and the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor. These receptors play a crucial role in regulation of Ca\textsuperscript{2+} influx associated with synaptic activity and modulation.\textsuperscript{56}
Choi et al. showed that prolonged exposure to high concentrations of glutamate leads to Ca\(^{2+}\)-dependent cell death in neuronal culture.

Activation of NMDA receptors by glutamate results in an increase in [Ca\(^{2+}\)]\(_{c}\). In addition, depolarization induces opening of voltage-gated Ca\(^{2+}\) channels, while the activity of the plasma membrane Na\(^+/\)Ca\(^{2+}\) exchangers is reversed. During this increase in [Ca\(^{2+}\)]\(_{c}\), mitochondria accumulate and retain Ca\(^{2+}\) to buffer the cytosolic loading. However, this increase in [Ca\(^{2+}\)]\(_{c}\) caused by glutamate promotes extensive accumulation of Ca\(^{2+}\) for several hours. In this context, it has been shown that necrosis is initiated by this delayed Ca\(^{2+}\) influx, which is independent of Ca\(^{2+}\) release from mitochondria, but dependent on declining activity of cytoplasmic Ca\(^{2+}\) clearing mechanisms (for example, calpain-mediated cleavage of Na\(^+/\)Ca\(^{2+}\) exchanger). Following the initiation of necrosis, mitochondria are overloaded with Ca\(^{2+}\), the electrochemical proton gradient collapses, and necrotic cell death is induced. Thus, it seems that alteration of this cellular response (for example, by a tumor or viral proteins) plays a role in the pathogenesis of human disorders. Prolonged permeability transition pore opening leads to a complete collapse of the membrane potential and Ca\(^{2+}\) release, which results in the complete loss of mitochondrial function and necrotic cell death.

**Mitochondrial impairment and psychiatric disorders**

Mitochondrial dysfunction has been studied in patients with brain diseases, including neurodegenerative diseases and psychiatric disorders. Evidence that patients with psychiatric disorders (depression, BD, and schizophrenia) exhibit mitochondrial abnormalities at the structural, molecular, and functional levels has been reviewed (Figure 1).

These findings suggest that a mitochondrial deficit is sufficient to trigger one or more psychiatric disorders. Mitochondrial deficits in psychiatric disorders are suggested by positron emission tomography (PET) analysis of brain energy metabolism. In addition, data suggesting a role for mitochondrial alterations in psychiatric disorders are only correlations; therefore, it remains to be determined whether these alterations contribute to the disease process or are just epiphenomena.

Interestingly, psychiatric symptoms have been observed in subjects with mitochondrial diseases. Fattal et al. identified 19 confirmed cases of mitochondrial disease with psychiatric complications, including BD, major depressive disorder, psychosis, anxiety disorders, and personality changes. Indeed, symptoms of mental illness have been previously documented in subjects affected by mitochondrial cytopathies. In addition, a case report of mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS), a typical mitochondrial encephalopathy, which had presented as mania prior to diagnosis, supports the role of mtDNA mutations in the etiology of psychiatric disorders.

Taken together, the reviewed lines of evidence, including ultrastructural, neuroradiological, biochemical, and genetic data, seem to point to a possible role of mitochondrial dysfunction in the pathological mechanism of some psychiatric disorders. However, the exact mechanisms by which deficits of energy metabolism occur in the brain of subjects affected with psychiatric disorders are not completely understood.

Mitochondrial dysfunctions (leading to decreased ATP production, oxidative stress, and apoptosis) occur in the early stages of different neurodegenerative diseases associated with mood disorders. Findings from genetic, postmortem brain, brain-imaging, and biomarker studies in humans with psychiatric disorders and rodent models of such disorders have confirmed this hypothesis.

**Depression**

Several lines of evidence suggest that mitochondrial dysfunction is an important component of the neurobiology of depression. Patients with depression have reduced glucose utilization in the prefrontal cortex, anterior cingulate gyrus, and caudate nucleus. The energy metabolism deficits observed in patients with depression may be widespread, as suggested by data that demonstrates reduced mitochondrial ATP production and increased mitochondrial DNA deletions as compared with control subjects.

![Figure 1](Image)

**Figure 1** Several events can compromise mitochondrial function and integrity. These include abnormal elevation of Ca\(^{2+}\), glutamate excitotoxicity, glutathione depletion, and altered gene expression of electron transport chain complexes. Additionally, the mitochondria are the main intracellular source of ROS, and ROS production contributes to mitochondrial dysfunction. Furthermore, mitochondrial dysfunction decreases ATP levels, causes apoptosis and oxidative stress, and inhibits ion pumps, and these changes are associated with psychiatric disorders. Akt = protein kinase B; AMPK = monophosphate-activated protein kinase; CIBP1 = C-terminal-binding protein 1; CO = carbon monoxide; mTOR = mammalian target of rapamycin; NF-κB = nuclear factor – κappa B; NO = nitric oxide; PKA = protein kinase A; PKC = protein kinase C; PI3K = phosphoinositide 3-kinase; ROS = reactive oxygen species.
Magarinos et al.\textsuperscript{72} found that stress did not affect the number of neuronal mitochondria; however, the total mitochondrial area increased after a stress paradigm, suggesting that longer duration of stress could compromise ATP synthesis. Gardner et al.\textsuperscript{73} showed a significant decrease of mitochondrial ATP production and mitochondrial enzyme content in muscle of patients with major depressive disorder. Madrigal et al.\textsuperscript{74} reported that complexes I-III and II-III of the mitochondrial respiratory chain were inhibited in the rat brain after chronic stress, as was brain Na\textsuperscript{+}, K\textsuperscript{+}-ATPase.\textsuperscript{75} Rezin et al.\textsuperscript{76} reported that mitochondrial respiratory chain complexes I, III and IV were inhibited in the cerebral cortex and cerebellum of rats after 40 days of chronic mild stress (CMS), and this was reversed by administration of ketamine.\textsuperscript{77} Gong et al.\textsuperscript{78} showed that exposure to CMS inhibited mitochondrial respiration and dissipated mitochondrial membrane potential. In addition, the mitochondrial ultrastructure was altered in brains of mice exposed to CMS.\textsuperscript{79}

Genetic evidence points to a role for mitochondrial impairment in depression. Postmortem brain tissue from a patient with severe depression was found to have more mtDNA deletions than postmortem muscle tissues from the same patient, suggesting that the accumulation of mtDNA deletions in the brain might play a role in the pathophysiology of depression.\textsuperscript{79}

**Bipolar disorder**

Several investigators have proposed that mitochondrial dysfunction is related to the pathophysiology of BD. Brain magnetic resonance spectroscopy has demonstrated decreased levels of N-acetyl-aspartate (a marker of mitochondrial energy production) in the prefrontal cortex of patients with BD as compared with healthy controls, indicating neurodevelopmental alterations in the former.\textsuperscript{80} Stork & Renshaw\textsuperscript{81} proposed a hypothesis of mitochondrial dysfunction in BD that involves impaired oxidative phosphorylation, a shift toward glycolytic energy production, a decrease in total energy production and/or substrate availability, and altered phospholipid metabolism. Postmortem studies have reported changes in mitochondrial-related gene expression in BD as well.\textsuperscript{82,83} In addition, manic-like hyperactivity induced by d-amphetamine, which is considered an animal model of mania, is associated with oxidative stress in the rat brain.\textsuperscript{84-86} Corrêa et al.\textsuperscript{87} showed that citrate synthase activity was inhibited in the rat hippocampus after mania induced by amphetamine, and this was reversed by valproate (VPA) and lithium (Li) administration. In contrast, Streck et al.\textsuperscript{88} demonstrated that amphetamine inhibited creatine kinase in rat brains, but VPA and Li were not able to prevent this. Zugno et al.\textsuperscript{89} showed that amphetamine increased Na\textsuperscript{+}, K\textsuperscript{+}-ATPase activity in rat brains, and that VPA or Li reversed this effect. Moreover, VPA and Li did not alter Na\textsuperscript{+}, K\textsuperscript{+}-ATPase activity. Valvassori et al.\textsuperscript{90} showed that AMPH inhibited mitochondrial respiratory chain activity in rat brains, and VPA, but not Li, reversed this. Feier et al.\textsuperscript{91} showed that methamphetamine inhibited the activities of Krebs cycle enzymes and complexes of the mitochondrial respiratory chain, and Li and VPA reversed methamphetamine-induced energy metabolism dysfunction.

Bachmann et al.\textsuperscript{92} have demonstrated that long-term treatment with Li and VPA enhanced cell respiration rate, mitochondrial membrane potential, and mitochondrial oxidation in SH-SY5Y cells. Additionally, methamphetamine reduces mitochondrial cytochrome c, mitochondrial antiapoptotic Bcl-2/Bax ratio, and mitochondrial cytochrome oxidase (COX) activity, and treatment with Li or VPA prevents these alterations. Treatment with Li or VPA prevented Bcl-2 attenuation of apoptosis by sequestering pro-caspases; preventing the release of mitochondrial apoptogenic factors, such as calcium, cytochrome c, and apoptosis-inducing factor, into the cytoplasm; and enhancing mitochondrial calcium uptake.\textsuperscript{93,94} Studies showed that upregulation of Bcl-2 is a result of the activation of extracellular signal-regulated kinase (ERK) and phosphoinositide 3-kinase (PI3K) pathways by mood stabilizers.\textsuperscript{95}

Patients with BD exhibit impaired brain energy metabolism, reduced levels of mitochondrial proteins involved in energy metabolism, and increased mtDNA mutations.\textsuperscript{96} A study using Southern blot analysis did not demonstrate mtDNA deletions in postmortem cerebral cortex samples of patients with mood disorders. When a highly sensitive quantitative PCR method was used, more mtDNA deletions were found in the brains of patients with BD than in control brains.\textsuperscript{97} Konradi et al.\textsuperscript{98} reported decreased expression of nuclear genes coding for the enzyme complexes responsible for oxidative phosphorylation and reduced expression of nuclear genes related to proteasome degradation in the hippocampus of nine subjects with BD.\textsuperscript{97} MacDonald et al.\textsuperscript{99} showed that creatine kinase mtRNA was decreased in patients with BD, mainly in the hippocampus. The inhibition of creatine kinase activity by amphetamine reinforces the hypothesis that metabolism impairment is involved in the pathophysiology of BD.

**Anxiety disorders**

Recent evidence demonstrates that impairment of cellular plasticity and resilience may underlie the pathophysiology of anxiety disorders, and that antidepressants have major effects on the signaling pathways that regulate neuroplasticity and cell survival.\textsuperscript{100,101}

It has been suggested that mitochondrial Ca\textsuperscript{2+} sequestration plays a key role in modulating the tone of synaptic plasticity in a variety of neuroanatomical regions, including those implicated in the pathophysiology of anxiety disorders.\textsuperscript{102} A study about the relative roles of mitochondrial and ER Ca\textsuperscript{2+} buffering showed that dendritic mitochondria rapidly accumulate Ca\textsuperscript{2+}, while the ER displays a more delayed increase in Ca\textsuperscript{2+} during high-frequency stimulation.\textsuperscript{103} Thus, it is possible that the regulation of mitochondrial function plays an important role in regulating the synaptic strength of the neuronal circuitry mediating complex behaviors.

Moreover, monoamine oxidase inhibitors (MAOIs), known for their anxiolytic and antidepressant properties,
improve mitochondrial function. The activation of mitochondrial benzodiazepine receptors reduced stress and anxiety in rats, and neurosteroids that had been widely recognized as having anxiolytic properties have specific binding sites on mitochondria and have been confirmed to modulate mitochondrial Ca\(^{2+}\) efflux and increase mitochondrial resilience.\(^{105-111}\)

Murphy et al.\(^{112}\) have shown in isolated mitochondria that Bcl-2 overexpression increases mitochondrial Ca\(^{2+}\) uptake capacity, increasing the resistance of mitochondria to Ca\(^{2+}\)-induced inhibition of respiration. Einat et al.,\(^{113}\) using BCL2-heterozygous mice, demonstrated an increase in anxiety-like behavior with reduced mitochondrial Bcl-2 levels, suggesting that mitochondrial function, modulated by Bcl-2, may be related to the regulation of anxiety behaviors, thus playing a critical role in the etiology of anxiety disorders.

**Obsessive-compulsive disorder**

Obsessive-compulsive disorder (OCD) is a common psychiatric disorder defined by the presence of obsessive thoughts and repetitive compulsive actions, and it often includes anxiety and depressive symptoms.\(^{114}\) Although the etiology of OCD remains unknown, the results of twin studies, familial studies, and segregation analysis have provided evidence that OCD has a strong genetic component.\(^{115-119}\)

Some investigators have also found markers of oxidative stress in the brain tissues of patients with OCD.\(^{120-122}\) Moreover, Kuloglu et al.\(^{120}\) showed significantly lower levels of vitamin E and C, and higher levels of malondialdehyde (MDA) in patients with OCD compared to controls, suggesting that OCD is linked to oxidative stress. Free radicals in the brain are mainly produced by catecholamine metabolism, and this increase in catecholaminergic metabolism seems to be associated with increased tissue damage.\(^{123,124}\) Depleted levels of glutathione (GSH) have also been found in postmortem prefrontal cortex samples of patients with psychiatric disorders.\(^{125}\) Diminished GSH levels affect mitochondrial function and inhibit the activity of the mitochondrial complexes, especially complex I.\(^{126}\)

Although no molecules that induce OCD symptoms have been identified, several neurotransmitters, including serotonin, dopamine, glutamate and gamma-aminobutyric acid (GABA), have been suggested to play regulatory roles in OCD. Neurotransmitters are highly redox-reactive molecules, and produce ROS during normal neurotransmission. Alterations in these neurotransmitter pathways may increase the oxidative burden in the brain.\(^{127}\) On the other hand, some investigators have suggested that dopamine also plays an important role in the pathogenesis of OCD.\(^{128,129}\)

In addition, a multivariate logistic regression analysis demonstrated that MnSOD, UCP2 I/D genotypes, and GSH had significant impacts on OCD. Prevalence differences between the genders of OCD patients have been previously reported.\(^{130-132}\) Yamada et al.\(^{132}\) showed that mitochondrial uncoupling protein 2 (UCP-2) regulates neurotransmission and that overexpression of UCP2 prevents dopamine transmission in the CNS. Knockdown of the UCP2 gene increases mitochondrial membrane potential and ROS production in murine endothelial cells.\(^{134}\) However, in transgenic mice, UCP-2 protects cells against apoptosis and oxidative stress. Walder et al.\(^{135}\) have suggested that a 45 bp insertion in UCP2 affects the amount and activity of UCP-2 protein by influencing mRNA stability, translation, and posttranslational modification. De Bilbao et al.\(^{136}\) suggested that resistance to cerebral ischemic injury in UCP2 knockout mice is regulated by mitochondrial GSH levels in microglia.

Although the pathology of mitochondrial disorders in OCD has not yet been identified, it is well known that mitochondrial dysfunction related to mutations of mitochondrial DNA or of nuclear-encoded genes linked to mitochondrially based oxidative phosphorylation leads to impaired energy metabolism, perturbs calcium homeostasis, and increases ROS and apoptosis.\(^{137-139}\) Changes that might influence neurotransmitter release, leading to OCD, since synaptic transmission requires high levels of ATP.

**Autism spectrum disorder**

Clinical, genetic, and biochemical evidence suggests that mitochondrial dysfunction in autism spectrum disorder (ASD) is more common than expected. Some patients with ASD phenotypes clearly have genetic-based primary mitochondrial disease.\(^{140}\)

ASD encompass severe developmental disorders characterized by variable degrees of impairment in language, communication, and social skills, as well as by repetitive and stereotypic patterns of behavior. Substantial percentages of autistic patients display peripheral markers of mitochondrial energy metabolism dysfunction, such as elevated lactate, pyruvate, and alanine levels in blood, urine, and/or cerebrospinal fluid, serum carnitine deficiency, and/or enhanced oxidative stress. These biochemical abnormalities are accompanied by highly heterogeneous clinical presentations, which generally encompass neurological and systemic symptoms that are relatively unusual in idiopathic autistic disorder. In some patients, these abnormalities have been successfully explained by the presence of specific mutations or rearrangements in their mitochondrial or nuclear DNA. However, in most cases, abnormal energy metabolism cannot be immediately linked to specific genetic or genomic defects. Recent evidence from postmortem studies of autistic brains points to abnormalities in the mitochondrial function as possible downstream consequences of dysreactive immunity and altered Ca\(^{2+}\) signaling.\(^{141}\)

The neurobiological basis for autism remains poorly understood. However, research suggests that environmental factors and neuroinflammation, in addition to genetic factors, are contributors.\(^{142}\) Recent evidence points to inflammatory mechanisms contributing to autism. Vargas et al.\(^{143}\) suggested that neuroinflammatory
processes are present in the autistic brain by showing that transforming growth factor (TGF-β1), interleukin (IL)-6 and IL-10 are increased in the brain of autistic patients. A number of studies have also shown that inflammatory cytokines, including tumor necrosis factor (TNF)-α, interferon (IFN)-γ, IL-1, IL-6, IL-8, and IL-12, are elevated in blood mononuclear cells, serum, plasma, and cerebrospinal fluid (CSF) of autistic subjects. Additionally, El-Ansary & Al-Ayadhi have shown that autistic patients have remarkably higher plasma HSP70, TGF-β2, caspase-7, and INF-γ levels as compared with age- and gender-matched controls, suggesting that these parameters confirm the role of neuroinflammation and apoptosis mechanisms in the etiology of autism, as well as the possibility of using these parameters as predictive biomarkers.

Mitochondria as a pharmacological target for psychiatric disorders

Mitochondria are an ideal target for therapeutic modification, because they are key regulators of energy production, ROS production, and apoptosis. Mitochondria-targeted drugs are therapeutic agents that can directly target mitochondria to address perturbed cellular bioenergetics, oxidative stress, mtDNA mutations, impaired mitochondrial Ca\(^{2+}\)-handling capacity, and mitochondrial-mediated apoptosis. However, mitochondria-targeted drugs can interact with mitochondria in a secondary manner, where primary targets are other cellular locations.

As mitochondria are also involved in initiating apoptotic cell decay, they are vulnerable targets for experimental and/or pharmacological interventions. Mood stabilizers also promote Bcl-2-related neuronal processes such as neurite outgrowth, adult hippocampal neuronal neurogenesis, and neuronal protection against a variety of insults. Thus, the members of the Bcl-2 protein family may mediate some of the behavioral effects of antidepressants, and pharmacological modulation of Bcl-2 function might produce antidepressant-like behavioral effects. Studies have shown that mice overexpressing Bcl-2-associated athanogene (Bag1) or Bax inhibitor 1 and mice that received brain infusions of the BID inhibitor BI-11A7 had a protective phenotype in several tests of depression-like behavior.

Furthermore, mice overexpressing Bax inhibitor 1 displayed resilience to monoamine depletion-induced anhedonia-like symptoms, and Bag1 transgenic mice showed resilience to amphetamine-induced hyperlocomotion. Besides, Zhu et al. demonstrated that mitochondrial Ca\(^{2+}\) depletion promotes apoptosis. In animal models of depression, inositol trisphosphate receptor inhibitors and other compounds that regulate mitochondrial Ca\(^{2+}\) influx produced behavioral effects similar to those produced by antidepressants, lithium, and ketamine. Additionally, nifedipine and nimodipine have produced promising results in treating and stabilizing mood in both animal models.

Figure 2 Mitochondria are commonly known for their important role in ATP synthesis through the electron transport chain. However, mitochondria also operate in different control systems, such as ROS metabolism and Ca\(^{2+}\) levels, to ensure cellular homeostasis. Such systems modulate the activity of key signaling pathways, which, in turn, regulate the expression and function of multiple nuclear co-regulators and transcription factors, triggering different responses and thus acting on synaptic plasticity and neurogenesis. ATP = adenosine triphosphate; ROS = reactive oxygen species.
models of depression and in humans with BD or other types of depressive disorder.\textsuperscript{162-165}

Considering that the mitochondrial permeability transition pore (mPTP) opens upon collapse of the mitochondrial membrane potential ($\Delta\Psi$), an mPTP inhibitor would be a good candidate for further testing. Kubota et al.\textsuperscript{166} showed that NIM811, an mPTP inhibitor, counteracted the behavioral phenotypes associated with BD in Polg1-transgenic mice. In addition, aminopropyl carbazole (P7C3) exerts its pro-neurogenic activity by protecting newborn neurons from apoptosis and inhibiting mPTP, and an mPTP inhibitor has demonstrated neuroprotective effects in vitro.\textsuperscript{167,168}

Some psychiatric medications already exhibit antioxidant activity.\textsuperscript{169-172} To protect mitochondria and the cell against such damaging effects, several measures can be applied. One is to increase the intracellular glutathione content. This can be done by supplying precursors for glutathione synthesis, such as $N$-acetylcysteine.\textsuperscript{173} A double-blind, placebo-controlled adjunctive study showed that the antioxidant $N$-acetylcysteine improved functioning and depressive symptoms in patients with BD after 24 weeks, compared with placebo treatment.\textsuperscript{174} Other compounds acting as general intracellular antioxidants include ascorbic acid (vitamin C), $\alpha$-tocopherol (vitamin E), $\beta$-carotene, and $\alpha$-lipoic acid.\textsuperscript{175,176} All these compounds are naturally present in the cell, but their levels can be increased by exogenous supplementation.

**Conclusions**

Mitochondria play a pivotal role in cellular energy metabolism. The final product of this process is ATP, used as a source of chemical energy. Besides this major role, mitochondria have been shown to be involved in other functions, such as signaling, calcium homeostasis, cellular differentiation, and cell death, as well as control of the cell cycle and of cell growth (Figure 2). Thus, understanding the interactions between mitochondrial dysfunction and development of psychiatric disorders, such as depression, BD, anxiety disorders, OCD, and ASDs, may help establish more effective therapeutic strategies for these psychiatric conditions and, consequently, enable better outcomes for affected subjects. Moreover, this evidence highlights the role of mitochondrial dysfunction in the pathophysiology of psychiatric disorders, which represents an interesting research prospect.

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**Disclosure**

The authors report no conflicts of interest.

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