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So Happy Together: The Storied Marriage Between Mitochondria and the Mind

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More than a billion years ago—or so the thinking goes—one of our single-celled ancestors happened to engulf a unicellular prokaryote. Like many couples that would follow them, the cells realized that life together—while not uncomplicated—was easier than life apart. As it turns out, the prokaryote was useful; it had figured out how to perform aerobic respiration to generate large amounts of energy in the form of adenosine triphosphate (ATP).

The two cells grew and reproduced together, with the endocytosed organism ultimately evolving into what we now know as the mitochondrion (Figure 1). Modern day mitochondria, like their single-celled ancestors, still have their own circular DNA, and each mitochondrion contains multiple copies of its own genome. But over time, mitochondria have transferred many of their genes to the nuclear genome, which now encodes most mitochondrial proteins (1).

Because of their unique role in generating ATP, mitochondria are vital to the functioning of all types of human cells, especially those that require large amounts of energy. Neurons in particular have high energy demands; although our brains only weigh about 3 pounds, they account for around 20% of our bodies' glucose and oxygen consumption (1,2).

The role of mitochondria in neurons is far more active than one might imagine. Mitochondria use microtubule networks to move around, making themselves available in regions of intense energy demand, including synapses and areas of neurite outgrowth. ATP produced by mitochondria is essential for loading neurotransmitters into synaptic vesicles and maintaining neuronal membrane potentials (3). Mitochondria are also involved in the regulation of intracellular calcium levels, which is crucial at synapses because calcium stimulates neurotransmitter release and facilitates many other processes (including gene transcription, the activation of second-messenger pathways, etc.) (2,3).

If mitochondria are necessary for these neuronal functions, it makes sense that mitochondrial damage can affect the nervous system. We see this play out in frank mitochondrial genetic

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illnesses, including mitochondrial epilepsy with ragged-red fibers and mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes, both of which have names that reflect their neurologic manifestations. We also see a higher than normal incidence of psychiatric illness in people with genetic mitochondrial disorders; it is estimated that about 54% of these patients suffer from major depression, 17% from bipolar disorder, and 11% from panic disorder (4). While a skeptic might say that this increased prevalence of psychiatric symptoms can be attributed to the stress of chronic illness, there is a growing body of evidence to suggest that mitochondrial impairment can cause psychiatric illness (2). For example, in a mouse model of a genetic mitochondrial disease, affected mice had depression-like episodes (4). All of which is to say that both neurologic and psychiatric symptoms are caused by diseases of the brain—a commonality we all too often forget.

While inherited mutations may be the most frequently discussed causes of mitochondrial impairment, an intriguing area of research is exploring the ways in which psychological stress and depression are associated with—and may even cause—mitochondrial dysfunction. Although we do not know exactly how this happens, researchers have proposed several possible mechanisms.

One hypothesis is that mitochondrial dysfunction is mediated by glucocorticoids, which can regulate mitochondrial gene expression and may be overproduced in states of stress and depression (2). Experiments with cultured mouse neurons suggest that short-term glucocorticoid exposure enhances mitochondria's abilities (including their capacity to regulate calcium), whereas long-term exposure is impairing (2). There are also data suggesting that people under chronic stress have less efficient mitochondria (5).

A separate hypothesis involves the idea of oxidative stress. This refers to the process by which reactive oxygen species (ROS)—including free radicals—can damage DNA, proteins, and lipids (6). Within our bodies, mitochondria and peroxisomes are the main sources of ROS (mitochondria generate ROS through the electron transport chain during ATP production). For reasons that are not well understood, biomarkers of oxidative stress appear to be increased in people with depression, and other mood and anxiety disorders have also been associated with oxidative stress (6,7). It may be that affective distress leads to a hypermetabolic state in which mitochondria go into overdrive and produce more ROS, or it might be that ROS are being used as signaling molecules (6).

Of note, ROS can be toxic to mitochondria. Mitochondrial DNA (mtDNA) is particularly vulnerable to oxidative damage; it does not have protective histones, and it also does not have the same repair mechanisms that are available to nuclear DNA. Thus, it acquires mutations easily (1). These mutations can render a mitochondrion unable to produce all the proteins it needs, leading to increased dysfunction and even more ROS production, thereby fueling a cycle of oxidative stress (6). Once mitochondria are significantly damaged, they can release proapoptotic factors that trigger cell death.

A growing body of clinical data is further elaborating potential connections between stress, depression, and mitochondria. One of the most striking studies was published in 2015 by Cai *et al.* (8), who collaborated with more than 60 other scientists to look at a cohort of 11,670

women from China. The group included women who had never been depressed and women with recurrent depression. Some of these women had survived extremely stressful experiences, including childhood sexual abuse.

When the investigators performed whole-genome sequencing on saliva samples from these thousands of women, they saw two major group differences. First, women with a history of stressful life experiences had an increased total amount of mtDNA. This finding is difficult to interpret but is thought to potentially reflect extracellular mtDNA that is released from cells after oxidative damage to mitochondria, or even cell death (7). The second finding was that women who had experienced stressful life events had shortened telomeres, which can be seen in settings of oxidative stress (7,8). Critically, on further analysis, these findings were driven entirely by the women who also had a history of depression: if you looked at only the nondepressed women, there was no connection between having a history of stressful life experiences and changes in mtDNA amount or telomere length (8).

Cai *et al.* (8) concluded that these changes were caused by stress plus the experience of depression. But why? Is it possible that stress acts on vulnerable mitochondria, causing cellular damage and triggering a cascade that leads to network-level disarray and depression? Or might stress take people who are prone to depression and trigger an overdrive state in which their mitochondria become overwhelmed? More succinctly: is mitochondrial dysfunction causing depression, or is depression causing mitochondrial dysfunction? Or might some other process be at play? At this point, there is no clear answer. And, of course, the question itself may be overly reductionist; it could be, for instance, that the two processes co-occur in a positive feedback cycle.

Regardless of the mechanisms involved, there is compelling evidence to suggest that mitochondrial (dys)function can play a role in psychiatric illness. As described in this mitochondriathemed issue of *Biological Psychiatry*, emerging work is exploring the potential connections between mitochondrial characteristics (e.g., gene variation, functional impairment, morphology) and neuropsychiatric illnesses such as bipolar disorder, autism spectrum disorder, Alzheimer's disease, Parkinson's disease, and—as discussed above—depression (1–3).

In addition, researchers are exploring treatments that might improve psychiatric symptoms by combating oxidative stress. The antioxidant coenzyme Q10—a free-radical scavenger and electron transport chain cofactor—has been proposed as a treatment for depression (2). *N*-acetylcysteine (another antioxidant) is likewise thought to ameliorate oxidative stress, and it seems to have some efficacy in treating bipolar depression (2). In a nonpharmacologic vein, evidence from mice suggests that physical exercise can improve both mitochondrial function and depressive/anxious symptoms (9).

Stepping back, it may be that mitochondria are involved in one of the most interesting recent stories in neuroscience—namely, our burgeoning understanding of synaptic health and dysfunction in depression. In depression, it is thought that neurons atrophy, synapses vanish, and dendrites shrink. Effective antidepressants—including not only medications, such as selective serotonin reuptake inhibitors and ketamine, but also exercise—have been shown to

reverse these deficits (10). That these morphologic changes are causally related to clinical improvement—enticing though this model may be—remains unproven.

Nonetheless, it is worth considering how such neuronal changes may occur. Pathways mediated by brain-derived neurotrophic factor are thought to be involved (9,10). It is easy to imagine that large amounts of energy would be required to create new neurons and synapses, so it is perhaps unsurprising that mitochondria may also play a role. Brain-derived neurotrophic factor is thought to stimulate the mitochondrial electron transport chain, and—as we know—mitochondria supply ATP and modulate calcium, facilitating synaptic activity and neuronal resilience (3,9). Thus, it may be that mitochondria help enact brain-derived neurotrophic factor's effects.

While much remains to be fleshed out, the broad theme is clear: the more we learn about mitochondria, the more they may be able to illuminate the shadowy spaces between neurotransmitters and mood states, genetic diatheses and psychiatric symptoms, and life experiences and mental health. They might be able to say a lot about who we are, and how we think and feel. After all, we have lived together for a long time.

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Figure 1.

Once glucose is converted to pyruvate through glycolysis, pyruvate enters the mitochondrion, where it is converted to acetyl coenzyme A (acetyl coA) in the mitochondrial matrix. Acetyl coA then enters the citric acid cycle (Krebs cycle) (A), which produces adenosine triphosphate (ATP), reduced nicotinamide adenine dinucleotide, and amino acid precursors. Situated in the inner mitochondrial membrane, the four complexes of the electron transport chain (labeled I–IV) (B) create a proton gradient across the inner mitochondrial membrane, enabling ATP synthase to create ATP through oxidative phosphorylation. Reactive oxygen species (ROS) (C) can be created as byproducts of the electron transport chain and can damage mitochondrial DNA. Antioxidants such as N-acetylcysteine (NAC) and coenzyme Q10 (CoQ10) can counteract the oxidizing effects of ROS. ADP, adenosine diphosphate; mtDNA, mitochondrial DNA.