Is bipolar disorder a mitochondrial disease?

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While we continue to refine our understanding of the pathophysiology of bipolar disorder (BD), a considerable distance remains before we establish a complete picture of the relevant processes and pathways that result in this illness. Recently, there has been a major focus on the neuroprotective effects of mood stabilizers and, hence, the cell loss and damage in specific brain regions in patients with BD.[1,2] This raises the question, what leads to the increasingly well-described pattern of neuronal damage and loss in this disease? Impairment of mitochondrial energy metabolism, one mechanism that is clearly important in many diseases of the brain, has recently become compellingly implicated in BD.[3] The evidence to support this mechanism comes from studies using diverse approaches. These data are briefly outlined below.

Both structural and functional MRI (fMRI) studies have identified specific brain regions in BD patients, namely, the prefrontal cortex and limbic regions, which appear to be altered in size and their function impaired.[4] fMRI studies have also revealed decreased pH, phosphocreatine and adenosine triphophate (ATP) levels and increased lactate levels in these brain regions, all of which are hallmarks of decreased energy metabolism.[5] Although these data do not specifically implicate mitochrondria, they clearly suggest energy imbalance in these brain regions. In a series of elegant experiments, Kato and Kato[6] identified abnormalities in mitochondrial DNA in patients with BD and further elaborated the contribution of several amino acid substitutions in specific candidate genes in several patient samples. Further, studies on gene coding for components of the electron transport chain are found both in mitochondrial and nuclear DNA, and significant associations with BD, including a gene on chromosome 18p11, which is a well-replicated chromosomal region in linkage studies of patients with BD, have been reported.[6]

Studies using DNA microarray techniques have demonstrated a remarkable concordance across several laboratories, with different patient samples identifying decreased expression of a cluster of genes in components of the mitochondrial electron transport chain in BD.[7–9] This technique, which is not limited by a specific hypothesis based on previous findings, allowed investigators to entertain novel ideas. The remarkable consistency between the results of these microarray studies is encouraging. Notwithstanding concerns that at least some of these changes relate to lower brain pH in at least some of the brain tissue samples that arise from differences in antemortem agonal factors, postmortem delay and storage of postmortem brain, that the mitochondrial abnormalities are remarkably evident in patients with BD, compared to other psychiatric disorders.[7] Since our laboratory reported some of these findings, I may be somewhat biased about the relevance of these findings.

Evidence from animal studies and cellular models on the molecular pharmacology of mood stabilizing drugs has also implicated mitochondrial energy metabolism as a target for these drugs. An earlier series of investigations showed that lithium and other mood stabilizers increased the expression of the antiapoptosis gene *Bcl-2*.[2] These were among the first studies to demonstrate a mitochondrial target for mood stabilizers. DNA microarray studies in animals examining targets of mood stabilizers, at least lithium and valproate, strongly suggested that these drugs increase energy metabolism and decrease oxidative damage and that these effects may be important for their efficacy in BD.[10] For instance, our laboratory has shown that the level and activity of glutathione, the major defence against oxidative damage in the brain and the activity of its metabolic enzymes, are increased by treatment with several mood stabilizers, thus enhances the brain's response to the insults that may occur in BD that involve altered energy metabolism.[10] Most of this evidence comes from the administration of mood stabilizers to animals under normal laboratory conditions. However, some of the most recent studies demonstrate that such effects are also observed under pathological conditions such as excitotoxicity and after oxidative stress.[11] The targets for these drugs are not identical to the markers found in patient samples. However, they suggest complimentary mechanisms that could prevent or compensate for the defects found in patients. For instance, enhancing glutathione defence could decrease potential oxidative

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damage resulting from mitochondrial defects or mutations in the electron transport chain.

Mitochondrial dysfunction has been long studied in other brain diseases, including neurodegenerative diseases and, to some extent, schizophrenia.[12,13] Several brain illnesses result from mutations in mitochondrial DNA, such as mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS), among others.[14] Fatal Leigh syndrome results from mutations in genes encoding for complex I and II proteins that are X-linked,[14] whereas Friedreich's ataxia is a disorder with trinucleotide repeat expansions in several enzymes in complexes I through III.[15] There is also good evidence of mitochondrial dysfunction in other neurodegenerative disorders (Alzheimer's disease, Huntington's disease, Parkinson's disease) that have mutations or defects in other proteins and pathways in which impaired energy metabolism contributes critically to the neurodegenerative processes.[12] In general, mitochondrial dysfunction contributes to neurodegeneration either by apoptosis or generation of reactive oxygen species (ROS). Closer to BD, there has been considerable discussion about oxidative stress contributing to the pathophysiology of schizophrenia and a recent focus on mutations in the enzyme glutamate cystein ligase modifier that would result in a decreased antioxidant response in this illness.[16]

It is possible that these new data will lead to a focus on BD as a metabolic disease — one in which energy metabolism becomes decreased, leading to subtle neuronal damage and cell death, which may be more evident in patients with chronic illness with lasting cognitive impairment. Treatment with mood stabilizers might ultimately enhance energy metabolism and reduce the damage of oxidative stress. In my opinion, these plausible ideas further refine our models of pathophysiology and place them in the "mainstream" of medicine and neuroscience.

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