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### MITOCHONDRIAL DYSFUNCTION AND OXIDATIVE STRESS IN BIPOLAR DISORDER

**A. Andreazza**

*Department of Psychiatry, University of British Columbia, Vancouver, Canada*

While we continue to refine our understanding of the pathophysiology of bipolar disorder (BD), several hypotheses have been postulated including a role for monoamines, gamma-amino butyric acid, glutamate, and second messenger signaling pathways. Recently, mitochondrial dysfunction and oxidative stress have been identified by a number of studies, as an important etiological factor in this disorder. Mitochondria play a crucial role in ATP production through oxidative phosphorylation, a process carried out by the electron transport chain (ETC) complexes. During the transfer of electrons along this ETC, the ROS can be generated, especially in complex I and III4. Growing body of evidence suggests the association of mitochondrial dysfunction and BD. Recent DNA microarray analysis in post-mortem frontal cortex and hippocampus revealed that the expression of several mRNAs coding for ETC complexes I-V subunits was decreased in subjects with BD. Supporting the key involvement of oxidative damage in BD, assays conducted with peripheral blood samples have demonstrated that BD is associated with alterations in antioxidant enzymes and increased lipid peroxidation. Recently we found that oxidative damage to lipid is present in the frontal cortex of BD subjects. A meta-analysis suggested that the levels of lipid peroxidation are elevated in BD providing support for oxidative stress hypothesis of BD. Furthermore, BD subjects showed increased DNA damage, as well as, upregulation of apoptotic genes. These data not only suggest that oxidative mechanisms may form unifying common pathogenic pathways in psychiatric disorders, but also introduce new targets for the development of therapeutic interventions.

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