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Review article

A model of the mitochondrial basis of bipolar disorder

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SUMMARY

Background: Bipolar disorder phenomenologically is a biphasic disorder of energy availability; increased in mania and decreased in depression. In consort, there is accumulating evidence indicating increased mitochondrial respiration and ATP production in bipolar mania which contrasts with decreased mitochondrial function in patients in the euthymic or depressive phase of the illness. Consequently, the central thesis of this paper is that bipolar disorder is due to a phasic dysregulation of mitochondrial biogenergetics. The elements responsible for this dysregulation may thus represent critical treatment targets for mood disorders, and are the subject of this paper.

Discussion: There are many potential mediators of mitochondrial function which collectively are implicated in bipolar disorder. Levels of oxidative stress, pro-inflammatory cytokines and intracellular calcium ions are all higher in bipolar mania than in the euthymic and depressive phases of the illness. Increased levels of calcium ions can partly account for increased oxidative phosphorylation via well documented pathways such as the modulation of the F_1–F_0 elements of ATP synthase. Likewise, increased levels of oxidative stress and pro-inflammatory cytokines lead to the upregulation of AMPK, SIRT-1, SIRT-3 and NAD^+ which directly stimulate oxidative phosphorylation. Uric acid and melatonin are also differentially elevated in bipolar mania and both molecules stimulate the production of ATP. The pro-apoptotic, neurotoxic and mitotoxic effects of elevated glutamate, dopamine and GSK-3 in bipolar mania may be counterbalanced by higher basal levels and activity of p53, Bcl-2, PI3K and Akt in an environment of elevated uric acid and decreased BDNF.

Summary: Details of these pathways are discussed as an explanatory model for the existence of increased ATP generation in mania. We also offer a model explaining the biphasic nature of mitochondrial respiration in bipolar disorder and the transition between mania and depression based on increasing levels of TNFα, ROS, NO, AMPK and SIRT-1 together with the antagonistic relationship between p53 and NF-κB.

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1. Introduction

Multiple lines of evidence indicate that mitochondrial dysfunction is a key element in the pathogenesis and pathophysiology of Bipolar Disorder (BPD; reviewed (Cataldo et al., 2010b; Clay et al., 2011; de Sousa et al., 2014a; Frey et al., 2007; Morris and Berk, 2015). Symptomatically, BPD is a biphasic disorder of energy availability; increased in mania and decreased in depression. Indices of increased mitochondrial respiration and ATP production in bipolar mania stand in contrast with decreased mitochondrial function in patients in the euthymic or depressive phase of the illness. The central thesis of this paper is that BPD results from a phasic dysregulation of mitochondrial bioenergetics. In particular, we propose that mitochondrial dysfunction may serve as a state dependent marker of the disorder, rather than a trait marker, with increased mitochondrial function being characteristic of, BPD mania while decreased mitochondrial function being characteristic of BPD depression, although trait dependent factors may be vulnerability markers. This paper aims to focus on the molecular pivots of this alternating dysregulation.

A substantial portion of such evidence has been provided via the use of 1H or 31P nuclear magnetic spectroscopy over a number of years, which have reported reduced N-acetyl aspartate (NAA) levels in BPD patients (Frey et al., 2007; Stork and Renshaw, 2005). These observations are highly significant as reduced levels of NAA are now generally accepted as a surrogate marker for cellular mitochondrial, metabolic and bioenergetic impairment rather than a specific maker for neural damage as once proposed. Readers interested in a detailed review of studies which have led to this consensus and a detailed treatment of the biochemistry underpinning NAA synthesis and function are invited to consult the work of Moffett et al. (2013) and Signoretti et al. (2010).

Numerous research teams have reported reduced levels of NAA in various regions of the brain in patients suffering from BPD (Stork and Renshaw, 2005). The majority of studies report reduced NAA in the hippocampus (Cecil et al., 2002; Deicken et al., 2003; Scherk et al., 2008) and the dorsolateral prefrontal cortex (Bertolino et al., 2003; Chang et al., 2003c). This general picture is supported by a meta- analysis of 22 studies involving 228 adults and 349 children (Yildiz-Yesiloglu and Ankerst, 2006). However a much larger meta-analysis involving 146 studies with 5643 participants pointed to a more inconsistent picture in which decreased NAA levels in the basal ganglia is the most consistent finding (Kraguljac et al., 2012). This contrasts with some prospective studies where authors failed to detect any abnormalities in NAA levels in that region (Hamakawa et al., 2004; Ohara et al., 1998) although it is fair to say that these authors were unable to detect low NAA levels in the prefrontal regions of their patients either. The reasons for these conflicting conclusions are not clear and interested readers are invited to consult the work of (Kraguljac et al., 2012) and (Ohara et al., 1998) for a consideration of the differences in their respective meta-analytical methodology as a potential explanation for the discrepancy in their findings.

Several research teams have reported the presence of deletions in mitochondrial DNA or reduced levels of mRNA encoding mitochondrial proteins such as the complex 1 subunit NDUFV-2 in the hippocampus and lymphoblastoid cells of BPD patients in various phases of the illness (Ben-Shachar and Karry, 2008; Konradi et al., 2004; Washizuka et al., 2009, 2005). Regionally specific complex 1 subunit abnormalities in NDUFV-1, NDUFV-2 and NDUFV-3 have been observed in the cerebellum of BPD patients but these are not observed in the striatum (Ben-Shachar and Karry, 2008). This pattern is the reverse of that seen in schizophrenia, where such abnormalities are seen in the striatum but not in the prefrontal cortex (Ben-Shachar and Karry, 2007). Other research teams have noted mitochondrial deletions and a general reduction in mRNA encoding proteins regulating a range of mitochondrial functions and ATP production in the cerebral cortex post mortem (Kato et al., 1994; Konradi et al., 2004). Sun and Barron (2006) reported a more widespread decrease in the expression of genes encoding proteins involved in the electron transport chain in the prefrontal cortex with many genes encoding complex III, IV and V downregulated. However another research team (Iwamoto et al., 2005) reported a global upregulation of these genes in medication free patients once the confounding effects of raised post-mortem pH and drug treatments such as sodium valproate and a range of typical and atypical neuroleptics, which are known to provoke mitochondrial dysfunction, were controlled for (Callaly et al., 2015). Hence the results of studies examining mitochondrial gene expression studies in the brain in BPD must be treated with caution if patients are on medication long term up to the point of death. There is also a growing consensus that data which does not control for the effects of post agonal pH post mortem may be problematic, as alterations in pH can also have a major suppressive effect on mitochondrial gene expression, for reasons which remain to be delineated (Li et al., 2004; Vawter et al., 2006).

The situation regarding mitochondrial gene expression profiles in peripheral immune cells extracted from BPD patients is also difficult to interpret. Naydenov et al. (2007) reported differences in electron transport chain (ETC) gene expression *in vivo* in response to glucose deprivation in lymphoblastic cell lines, which is broadly supportive of the work of (Washizuka et al., 2009) and others cited above. However, Beech and fellow workers reported a significant upregulation of genes encoding complex I, II, III, IV, and V of the ETC in freshly extracted peripheral blood mononuclear cells (PBMCS) from BPD patients, calling into question the validity of extrapolating from cell lines into *in vivo* conditions (Beech et al., 2010). The use of proteomic techniques revealed abnormal signatures of proteins involved in mitochondrial function, glycolysis and gluconeogenesis in the hippocampus of BPD patients, although it is not clear