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Perspective

Mitochondrially Mediated Plasticity in the Pathophysiology and Treatment of Bipolar Disorder

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Bipolar disorder (BPD) has traditionally been conceptualized as a neurochemical disorder, but there is mounting evidence for impairments of cellular plasticity and resilience. Here, we review and synthesize the evidence that critical aspects of mitochondrial function may play an integral role in the pathophysiology and treatment of BPD. Retrospective database searches were performed, including MEDLINE, abstract booklets, and conference proceedings. Articles were also obtained from references therein and personal communications, including original scientific work, reviews, and meta-analyses of the literature. Material regarding the potential role of mitochondrial function included genetic studies, microarray studies, studies of intracellular calcium regulation, neuroimaging studies, postmortem brain studies, and preclinical and clinical studies of cellular plasticity and resilience. We review these data and discuss their implications not only in the context of changing existing conceptualizations regarding the pathophysiology of BPD, but also for the strategic development of improved therapeutics. We have focused on specific aspects of mitochondrial dysfunction that may have major relevance for the pathophysiology and treatment of BPD. Notably, we discuss calcium dysregulation, oxidative phosphorylation abnormalities, and abnormalities in cellular resilience and synaptic plasticity. Accumulating evidence from microarray studies, biochemical studies, neuroimaging, and postmortem brain studies all support the role of mitochondrial dysfunction in the pathophysiology of BPD. We propose that although BPD is not a classic mitochondrial disease, subtle deficits in mitochondrial function likely play an important role in various facets of BPD, and that enhancing mitochondrial function may represent a critical component for the optimal long-term treatment of the disorder.

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INTRODUCTION

Despite the fact that bipolar disorder (BPD) is a common, severe, often life-threatening illness, the biochemical abnormalities underlying the predisposition to, and the pathophysiology of, this complex and intriguing neuropsychiatric disorder have yet to be fully elucidated (Goodwin and Jamison, 2007). The brain systems that have heretofore received the greatest attention in neurobiological studies of BPD have been the monoaminergic neurotransmitter systems, which are extensively distributed throughout the network of limbic, striatal, and prefrontal cortical neuronal circuits thought to support the behavioral and visceral manifestations of the disease (Drevets, 2000). Neurobiological studies of mood disorders over the last 40 years have primarily focused on abnormalities of these systems, on characterizing alterations of individual neurotransmitters in disease states, and on assessing response to mood stabilizer and antidepressant medications. Studies of cerebrospinal fluid chemistry, neuroendocrine responses to pharmacological challenge, and neuroreceptor and transporter binding have demonstrated a number of abnormalities in monoaminergic neurotransmitter and neuropeptide systems in mood disorders (Goodwin and Jamison, 2007).

Unfortunately, these observations have not yet greatly advanced our understanding of the underlying biology of recurrent mood disorders, which must include an explanation for the predilection to episodic, and often profound, mood disturbance that can become progressive over time. BPD likely arises from the complex interaction of multiple susceptibility (and protective) genes and environmental factors, and the phenotypic expression of the disease includes not only mood disturbance, but also a constellation of cognitive, motor, autonomic, endocrine, and sleep/wake

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abnormalities. Furthermore, while most antidepressants exert their initial effects by increasing intrasynaptic levels of serotonin and/or norepinephrine, their clinical antidepressant effects are observed only after chronic administration (over days to weeks), suggesting that a cascade of downstream events is ultimately responsible for their therapeutic effects. These observations have led to the idea that while dysfunction within the monoaminergic neurotransmitter systems is likely to play an important role in mediating some facets of the pathophysiology of BPD, it likely represents the downstream effects of other, more primary abnormalities in signaling pathways.

Plasticity, the ability to undergo and sustain change, is essential for the proper functioning of our nervous system. This capacity for change allows organisms to adapt to complex alterations in both their internal and external environments, a feature fundamentally important for survival and reproduction. The biological basis of this capacity to adapt encompasses a diverse set of cellular and molecular mechanisms that fall under the general term 'neuroplasticity'; in this paper, we make the distinction between synaptic plasticity and neuroplasticity.

Synaptic plasticity refers to the cellular process that results in lasting changes in the efficacy of neurotransmission. More specifically, the term synaptic plasticity refers to the variability of the strength of a signal transmitted through a synapse. The regulation of transmission at the synapse may be mediated by changes in neurotransmitter levels, receptor subunit phosphorylation, surface/cellular levels of receptors, and conductance changes, among others.

Neuroplasticity is a broader term that encapsulates changes in intracellular signaling cascades and gene regulation, modifications of synaptic number and strength, variations in neurotransmitter release, modeling of axonal and dendritic architecture and, in some areas of the CNS, the generation of new neurons. Modifications arising from neuroplastic mechanisms can be of short duration or long lasting, and this is determined by the qualitative, quantitative, and temporal characteristics of the precipitating stimuli.

Research on the biological underpinnings of mood disorders has therefore moved away from focusing on absolute changes in neurochemicals such as monoamines and neuropeptides, and instead has begun highlighting the role of neural circuits and synapses, and the plastic processes controlling their function. Thus, these illnesses can best be conceptualized as genetically influenced disorders of synapses and circuits rather than simply as deficits or excesses in individual neurotransmitters (Bachmann *et al*, 2005; Schloesser *et al*, 2007). Most germane to the present discussion is the fact that it is now clear that mitochondria regulate not only long-term cell survival/cell death, but also immediate synaptic function—both of which are clearly very relevant for BPD. Indeed, Kato and co-workers had anticipated some of the recent developments in the field when they first proposed that mitochondrial dysfunction might play an important role in the pathophysiology of BPD (Kato and Kato, 2000; Kato *et al*, 2001; Murashita *et al*, 2000).

It is important to emphasize at the outset that it is not our contention that BPD is necessarily a classic mitochondrial disorder. Indeed, the vast majority of BPD patients do not show the symptoms of classic mitochondrial disorders (eg, optic and retinal atrophy, seizures, dementia, ataxia, myopathy, exercise intolerance, cardiac conduction defects, diabetes, and lactic acidosis; Fadic and Johns, 1996). Instead, emerging data suggest that upstream abnormalities (likely encoded in the nucleus) converge on mitochondrial function, leading to altered synaptic plasticity and impaired cellular resilience. In this paper, we synthesize and focus on the emerging data that support the contention that mitochondrial dysfunction may play a role in the impairments of cellular plasticity and resilience manifest in the context of BPD. It should be noted that it is beyond the scope of this paper to discuss in detail the myriad functions performed by mitochondria. Thus, we limit ourselves to a discussion of those facets most likely to play a role in the pathophysiology and treatment of BPD, namely intracellular calcium regulation, cytoprotection, and synaptic plasticity.

MITOCHONDRIA PLAY CRITICAL ROLES IN INTRACELLULAR Ca^{2+} REGULATION, CYTOPROTECTION, AND REMODELING NEUROPLASTICITY

Mitochondrial physiology has the well-known function of energy production through the Krebs tricarboxylic acid cycle and oxidative phosphorylation. One byproduct of oxidative phosphorylation is the production of reactive oxidative species (ROS) that are capable of reacting with a wide variety of biological substrates, including protein thiol groups, membrane lipids, and nucleic acids, leading to cell damage and mutations.

However, mitochondria have additional important roles in the regulation of intracellular calcium (Ca^{2+}), cytoprotection, and synaptic plasticity. Mitochondrial Ca^{2+} uptake from and release into the cytosol has important consequences for neuronal and glial activity, modulating both physiological and pathophysiological intracellular responses (Simpson and Russell, 1998). Calcium ions influence the synthesis and release of neurotransmitters, receptor signaling, the action potential, and neuronal periodicity (Kandel *et al*, 2000; Torok, 1989; Wolff *et al*, 1977). The diffusion of free Ca^{2+} ion in subcellular regions is normally discrete and short-lived (it is estimated to be free for $\sim$50 ms before encountering a Ca^{2+}-binding protein); it is then sequestered in the mitochondria and endoplasmic reticulum (ER).

A large movement of positively charged Ca^{2+} into the mitochondrion will exert a depolarizing effect; most importantly for the present discussion, this increase can surpass mitochondrial capacity to export protons (as well as other cations), and it has the potential to lead to the cessation of ATP synthesis and the initiation of the apoptotic (programmed cell death) process (see below). On *N*-methyl-D-aspartate (NMDA) glutamate receptor activation, channel opening allows a rapid influx of Ca^{2+} into the cytosol and mitochondria that are able to rapidly buffer this load (Nicholls and Ward, 2000; Stout *et al*, 1998). Ca^{2+} uptake into mitochondria may activate the permeability transition pore (PTP, a channel crossing the outer and inner mitochondrial membranes) independently of ROS production (Chalmers and Nicholls, 2003; Figure 1).

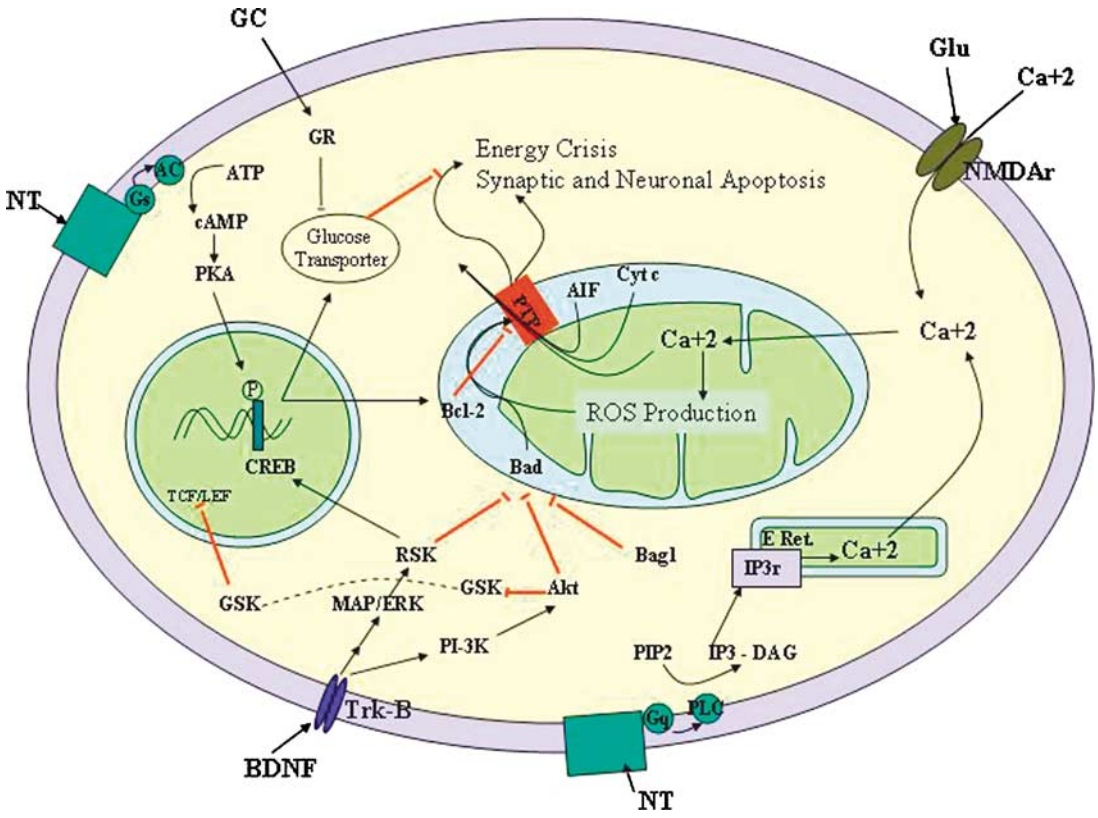

Figure 1 Intracellular signaling pathways relevant to the pathophysiology of BPD and its role in synaptic and neuronal apoptosis. Several neurotransmitters exert their action through G protein-coupled receptors associated with PLC, which is involved in the PIP2 intracellular pathway; IP3 and DAG acting on the endoplasmic reticulum modify the intracellular concentration of Ca^{2+}. Glutamate activation of NMDA receptors also induces a rapid influx of Ca^{2+} into the cytosol and subsequently, mitochondria. A large movement of positively charged Ca^{2+} into the mitochondrion will exert a depolarizing effect, surpassing mitochondrial capacity to export protons (as well as other cations), potentially leading to the cessation of ATP synthesis and the activation of the permeability transition pore—independently of ROS production—initiating apoptotic processes. The figure also depicts the neuroprotective role of the activation of G protein-coupled receptors associated with the activation of the PKA intracellular pathway, which mediates the phosphorylation and activation of CREB and upregulates bcl-2—an antiapoptotic protein that acts by increasing the stability of the PTP. Similar upregulation of bcl-2 occurs through the activation of Trk-B receptor by BDNF, through the MAP/ERK pathway, in addition to the interference against propapototic mitochondrial proteins (such as Bad). AC, adenylyl cyclase; AIF, apoptosis-inducing factor; Akt, protein kinase that inactivate GSK; ATP, adenosine triphosphate; Bad, pro-apoptotic protein regulated by RSK; Bag-1, bcl-2-binding antiapoptotic protein; bcl-2, antiapoptotic protein B-cell leukemia/lymphoma; BDNF, brain-derived neurotrophic factor; Ca^{2+}, calcium; cAMP, cyclic adenosine monophosphate; CREB, cAMP response element-binding protein; Cyt c, cytochrome C; DAG, diacylglycerol; E Ret, endoplasmic reticulum; GC, glucocorticoid; Glu, glutamate; GR, glucocorticoid receptor; Gs, protein G stimulatory of adenylyl cyclase; GSK, glycogen synthase kinase; Gq, protein G stimulatory of phospholipase C; IP3, inositol 4,5-trisphosphate; IP3r, inositol triphosphate receptor; MAP/ERK, mitogen-activated protein kinase (MAP) pathway also referred to as extracellular signal-regulated kinase (ERK) pathway; NMDAr, *N*-methyl-D-aspartate receptor; NT, neurotransmitter and its G protein-coupled receptor; P, phosphate group; PIP2, phosphatidylinositol biphosphate; PI-3K, phosphatidylinositol 3-kinase; PKA, protein kinase A; PLC, phospholipase C; PTP, permeability transition pore; ROS, reactive oxidative species; RSK, kinase of ERK-MAP kinase cascade that downregulates Bad; TCF/LEF, transcription factors for specific genes; Trk-B, tyrosine kinase receptor.

The opening of the PTP has a number of important consequences including not only contributions to learning and synaptic plasticity (Weeber *et al*, 2002), but also cell death (Bernardi *et al*, 1998). Mitochondria immediately depolarize (stopping or reversing ATP synthesis) and a number of proteins are released from the intermembrane space. These include the proteins cytochrome c and apoptosis-inducing factor (AIF), which are known to lead to the activation in the cytosol of proteases (caspases). It is believed that this release is the first irreversible step of apoptosis, after which the cell is committed to undergo programmed cell death. Intriguingly, mounting evidence suggests that activation of mitochondrial apoptotic cascades may lead to a process of 'synaptic apoptosis' activated in a highly localized manner (Culmsee and Mattson, 2005). Subsequently, individual synapses or neurites may selectively undergo atrophy and provide a mechanism for synapse loss in both physiological and pathophysiological processes. Apoptotic signaling in the synaptic compartment appears to have some synapse-specific effects, such as the degradation of certain glutamate receptors (Glazner *et al*, 2000).

Importantly, a growing body of evidence suggests mitochondria may be integrally involved in the general processes of synaptic plasticity (Yang *et al*, 2003). The depolarization of presynaptic mitochondria has been shown to impair neurotransmitter release following tetanic stimulation (likely through the disruption of intracellular Ca^{2+} buffering; Billups and Forsythe, 2002). In addition, increased synaptic activity has been shown to induce the expression of mitochondrial-encoded genes, suggesting that a long-lasting upregulation of energy production may be triggered by synaptic activity itself, thereby playing a role

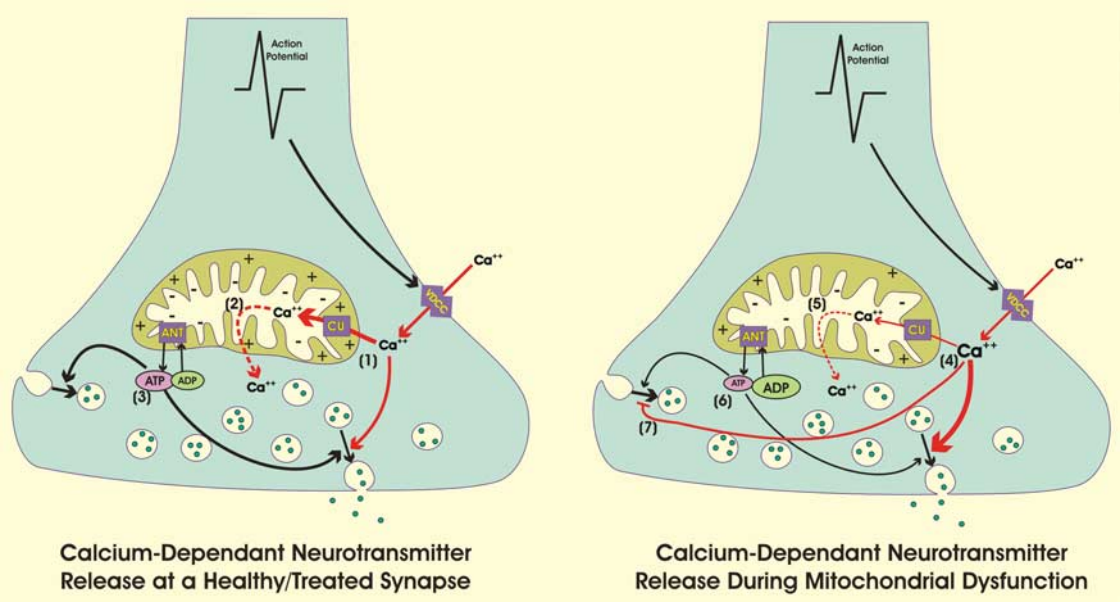

Figure 2 The putative role of mitochondria in synaptic plasticity and possible consequences of mitochondrial pathology and/or treatment. Under healthy conditions (left side), the mitochondrion exerts several effects on presynaptic neurotransmitter release. The surge in intracellular calcium during an individual action potential is rapidly buffered by MMP-driven mitochondrial calcium uptake (1). The slow release of calcium back into the cytoplasm is thought to allow for post-tetanic potentiation (2). The continuous production of ATP and removal of ADP is essential for the energy demanding processes of vesicle docking, fusion, and endocytosis (3). Under pathological conditions (right side), many of these processes may be disrupted. Failure of the MMP reduces the calcium uptake affinity, thereby resulting in more pronounced calcium spikes and chaotic, desynchronized release (4). The return of mitochondrial calcium to the cytoplasm is subsequently impaired, possibly resulting in deficient post-tetantic potentiation (5). Failure of the MMP would also lead to a reduction in ATP production, resulting in more rapid fatigue of energy-dependant processes (6). Finally, abnormally elevated cytosolic calcium may inhibit the efficiency of endocytosis, further impairing subsequent release (7). ANT, adenine nucleotide translocase; ADP/ATP, adenosine di-/tri-phosphate; CU, calcium uniporter; MMP, mitochondrial membrane potential; VDCC, voltage-dependant calcium channel.

in the long-term regulation of synaptic strength (Williams *et al*, 1998; for a review see Mattson and Liu, 2003; Figure 2). Thus, long-term mitochondrial dysfunction is associated with cell death, whereas more subtle mitochondrial dysfunction is associated with 'here and now' synaptic dysfunction.

THE ROLE OF BCL-2 PROTEINS IN THE MITOCHONDRIA: CRITICAL ARBITERS OF CELLULAR PLASTICITY AND RESILIENCE

As we discuss in more detail later, the bcl-2 family of proteins are major targets for the actions of mood stabilizers; here, we provide a brief overview of their roles in regulating mitochondrial function. The bcl-2 family of proteins consists of both pro- and antiapoptotic proteins embedded in the inner mitochondrial membrane. They may also be present in nuclear membranes and in the ER. Thus, the expression and/or activation of proapoptotic bcl-2 family members (eg, bad and bax) increase mitochondrial membrane permeability, whereas the antiapoptotic members (eg, bcl-2 and bcl-xl) have the opposite effect. The most commonly observed effects of these antiapoptotic proteins are reductions in ROS production, the prevention of PTP opening, and, thus, mitochondrial depolarization (Zamzami *et al*, 1998). Notably, studies of isolated mitochondria have shown that bcl-2 overexpression increases mitochondria Ca^{2+} uptake capacity (Murphy *et al*, 1996), making the cells appear particularly resistant to the destructive influence of elevated intracellular Ca^{2+}. Thus, bcl-2 may exert significant effects on cellular Ca^{2+} buffering, under the extreme conditions of Ca^{2+}-induced apoptosis and potentially even during normal synaptic activity.

MITOCHONDRIAL GENETICS

Mitochondria are unique in that they are the only organelle to contain nonnuclear genetic information. Mitochondrial DNA (mtDNA) encodes 13 proteins, all components of the electron transport chain, as well as transfer and ribosomal RNAs, which suggests that mitochondria synthesize proteins independently of the mechanism used for nuclear genes; it should be noted, however, that the vast majority of proteins present in the mitochondrion are coded in the nucleus. Mitochondria have the unique properties of maternal inheritance and heteroplasmy. Heteroplasmy refers to the fact that different cells contain different numbers/types of mitochondria; thus, mitochondrial dysfunction may manifest in a very regional-specific manner. Partly because the female gamete contains vastly more cytoplasm (and therefore mitochondria) than the male gamete, the mtDNA of offspring is almost exclusively maternal in origin. Pertinent to the present discussion, it is noteworthy that some previous studies have noted a parent-of-origin effect in BPD (a pattern of maternal transmission; McMahon *et al*, 1995; Stine *et al*, 1995). It is also worth noting that mtDNA mutations occur at a much higher frequency than nuclear DNA mutations, likely owing to a

combination of closer proximity to free radical production and less efficient DNA repair mechanisms (Richter *et al*, 1988). We now turn to a discussion of those aspects of mitochondrial function that have most relevance to the pathophysiology and treatment of BPD.

CALCIUM DYSREGULATION IN BPD: POTENTIAL ROLE FOR MITOCHONDRIAL CALCIUM-SEQUESTRATION MACHINERY

Impaired regulation of Ca^{2+} cascades is one of the most reproducible biological abnormalities described in BPD research (Tables 1 and 2). Studies have consistently revealed elevations in basal intracellular Ca^{2+} levels in platelets, lymphocytes, or neutrophils of patients with BPD. Higher platelet intracellular Ca^{2+} elevations have also been found in BPD patients in response to stimulation with thrombin, platelet activator factor (PAF), serotonin, dopamine, and thapsigargin when compared with healthy volunteers or unipolar depressive patients (Table 1). Similarly, higher elevations have been observed in lymphocytes when the cells were stimulated with phytohemagglutinin, concavalin A, thrombin, and, as in platelets, with thapsigargin and serotonin (Table 2). The fact that Ca^{2+} dysregulation is observed in response to such diverse stimuli suggests that the abnormality is not simply due to the activity of specific receptors, but rather due to a 'downstream' function. These observations strongly suggest that calcium release or sequestration (eg, by mitochondria) may represent a site

Table 1 Intracellular Calcium in Blood Elements of Bipolar Patients: platelets

Reference	Basal-stimulation	Intracellular Ca level (*N*, sample size)	Treatment status
Bowden *et al* (1988)	Basal	BD (14) > UD (29) ($p = 0.05$) Note that BD = C (10) and UD = BM (11)	Untreated
Dubovsky *et al* (1989)	Basal	BM (15) > C (15) ($p = 0.0022$)	Untreated and recovered
	PAF/thrombin BM	BD (15) > BE (13) ($p = 0.0001$) = UD (13), C	
Tan *et al* (1990)	Basal	BE (6) > C (7) ($p = 0.0001$)	Li treated
	Thrombin	BE > C ($p = 0.02$) (with or without *in vitro* Li incubation)	
Dubovsky *et al* (1991)	Basal	BD (15) > UD (9), C (13) = BE (9) ($p < 0.01$)	Untreated and treated
	Thrombin	BD > UD, C ($p < 0.01$)	
Dubovsky *et al* (1992)	Basal	BM (4), BD (5) > C (7) ($p < 0.0009$)	Untreated
Kusumi *et al* (1992)	Basal	BD (14) = UM (23) = UN (16) = C (25)*	Untreated
	Thrombin	BD > UM, UN, C ($p < 0.05$)	
Kusumi *et al* (1994)	Basal	BD (16) = UM (26) = UN (18) = C (30)*	Untreated
	5-HT	BD, UM > UN, C ($p < 0.05$)	Untreated and remitted
Berk *et al* (1994)	Basal	BM (21), BD (19), BE Li treated (20) > C (20) ($p < 0.01$)	Treated
	Dopamine	Elevated in all groups ($p < 0.0001$), no inter-group differences	
Dubovsky *et al* (1994)	Basal	BP or SAP (7), BM (2), C (9)	Not reported
		Plasma of patients does not alter Ca in platelets of C	
Bothwell *et al* (1994)	Basal	BP (17) = UP (27) = C (44)*	Treated
	5-HT/PAF	BP (17) = UP (27) = C (44)*. Li treated > C ($p < 0.014$)	
Tan *et al* (1995)	Basal	BM (7) = C (26)*	Haloperidol treated
	Thrombin	BM (7) > C (26)*	
Okamoto *et al* (1995)	Basal	Untreated BM (10) > BE Li-CBZ treated (10), C (14) ($p < 0.01$)	Untreated and treated
	5-HT	Untreated BM > BE Li-CBZ treated, C ($p < 0.01$)	
Yamawaki *et al* (1996)	Basal	BD (13) = UP (12) = C (15)*	Untreated
	5-HT	BD, UD > C ($p < 0.01$)	
Hough *et al* (1999)	Basal	BP > C (14) ($p = 0.0046$)	Untreated and treated
	Thrombin/5-HT/TGN	BP > C ($p < 0.05$)	
Kusumi *et al* (2000)	Basal	BP (24) = UM (51) = UN (23)*	Untreated
	5-HT	BP > C ($p < 0.005$)	
Suzuki *et al* (2001)	Basal	BP (20) = UM (26) = UN (16) = C (30)	Untreated
	5-HT	BP > C ($p = 0.0134$)	

Abbreviations: BD, BP depressed; BE, BP euthymic; BM, BP manic; BP, bipolar patient; C, controls (healthy volunteers); CBZ, carbamazepine; Li, lithium; PAF, platelet-activator factor; SAP, schizoaffective patients; TCA, tricyclic antidepressant; TGN, thapsigargin; UD, unipolar depressed patient; UM, unipolar melancholic patient; UN, unipolar depressed not melancholic patient; 5-HT, serotonin.
*Difference not statistically significant.

Table 2 Intracellular Calcium in Blood Elements of Bipolar Patients: lymphocytes

Reference	Basal-stimulation	Intracellular Ca level (*N*, sample size)	Treatment Status
Dubovsky *et al* (1992)	Basal	BM (4), BPD (5) > C (7) ($p<0.0009$)	Untreated
van Calker *et al* (1993)	Basal not shown fMLP	BE (9) Li treated, BP (14) untreated, C (10) BE treated > C > BP untreated ($p<0.05$)	Untreated and treated
Dubovsky *et al* (1994)	Basal PHG, Concavalin A	BP (26) > C (7) ($p<0.005$) BP > C* CBZ lowered Ca basal and Ca stimulated in BP ($p=0.004$), not in C*	Treated
Forstner *et al* (1994)	Basal in neutrophils fMLP	C (14) = Li treated (14) BP or UP* Li treatment lowered Ca response < C ($p<0.05$)	Treated
Emamghoreishi *et al* (1997)	BLCL Basal T ly Basal PHG	BP I (28) > C (20) ($p<0.05$). BP II (11) = UP (14) = C Male BP I > C ($p<0.05$). BP II = UP = C BP I, UP < C ($p<0.05$)	Untreated and treated
Hough *et al* (1999)	Basal Thrombin, 5HT, TGN	BP (34) > C (14) ($p=0.0138$) BP > C only with TGN ($p=0.002$)	Untreated and treated

Abbreviations: BD, BP depressed; BE, BP euthymic; BLCL, immortalized B lymphoblasts cell line; BM, BP manic; BP, bipolar patient; C, controls (healthy volunteers); CBZ, carbamazepine; fMLP, formylmethionylleucylphenalanin; Li, lithium; PHG, phytohemaglutinin; T ly, lymphocytes T; TGN, thapsigargin; UP, unipolar depressed patient; 5-HT, serotonin.
*Difference not statistical significant.

of dysfunction in BPD. However, it is conceivable that the above-mentioned anomalies in peripheral cells are simply the consequence of the myriad other abnormalities of circulating factors (eg, catecholamines or glucocorticoids).

To address this potential confound, Warsh and co-workers used Epstein–Barr-virus-immortalized B lymphoblasts (BLCL) that they had grown in culture for weeks, thus elegantly removing the patients' confounding circulating environment (Yoon *et al*, 2001). They found that even in the immortalized lymphoblasts, BPD patients showed elevated basal Ca^{2+} concentration compared with healthy subjects or patients with other psychiatric disorders. In an extension of these studies, they investigated the components of the storage-operated Ca^{2+} entry (SOCE), and found a reduction in the mRNA expression of the TRPC7 (TRPM2) gene (whose gene product is implicated in SOCE functioning) in BLCLs from a subgroup of BPD I patients (Yoon *et al*, 2001). This refined work suggests that some calcium abnormalities in BPD are state-independent. As a corollary, it is now important to further delineate the specific nature of these abnormalities, their relationship to illness-state and their pathophysiological significance.

Most recently, Kato and associates (2003) investigated cytosolic and mitochondrial Ca^{2+} responses in lymphoblastoid cells from BPD subjects. They found that the thapsigargin-induced cytosolic Ca^{2+} response was significantly higher in patients with BPD (thapsigargin facilitates release of intracellular calcium, thereby bypassing specific receptors). Furthermore, using a mitochondrial uncoupler that abolishes mitochondrial Ca^{2+} uptake, they observed that responses differed significantly between mitochondrial DNA haplotypes reported to be associated with BPD (Kato *et al*, 2003). Together, these results clearly suggest that mitochondrial calcium regulation contributes to the Ca^{2+} abnormalities seen in BPD.

In addition to the mitochondrial contribution to intracellular Ca^{2+} regulation, Kato and co-workers identified XBP1, a pivotal gene in ER stress response, as contributing to the genetic risk factor for BPD (Kakiuchi *et al*, 2003). They demonstrated the impaired XBP1 expression after inducing ER stress associated with the polymorphism; these effects were countered by the mood stabilizer valproate (VPA). Finally, they observed that the XBP1C/G genotype was significantly associated with higher stress response in lymphoblastoid cells lines (Kakiuchi *et al*, 2003). Interestingly, another study that used a similar approach also noted decreased expression levels of NDUFV2 gene (a nuclear-encoded mitochondrial complex I subunit gene) in lymphoblastoid cells from BPD patients (Washizuka *et al*, 2003). Although these findings await independent replication, they are important in view of the growing body of evidence demonstrating that subcellular compartmentalization of Ca^{2+} and its source may be large determinants of neural 'toxicity' (Mattson *et al*, 2001; Sapolsky, 2000; Figure 1). It should be emphasized that here we refer not to the neural 'life and death' observed in classical neurodegenerative diseases, but to the more subtle atrophic changes observed in BPD, such as those associated with Ca^{2+} regulation phenomena (discussed in greater detail below).

COULD IMPAIRMENTS OF CELLULAR PLASTICITY AND RESILIENCE BE ASSOCIATED WITH MITOCHONDRIAL DYSFUNCTION IN BPD?

Although BPD is not a classical neurodegenerative disorder, structural neuroimaging studies have demonstrated regional volumetric reductions; these include reduced gray matter volumes in areas of the orbital and medial prefrontal cortex (PFC), temporal lobe, and enlargement of the third ventricle (reviewed by Manji *et al*, 2003). Recent postmortem neuropathological studies are complementary, showing reductions in cortex volume, region- and layer-specific reductions in number, density, and/or size of neurons and glial cells in the subgenual PFC, orbital cortex, dorsal anterolateral PFC, amygdala, and in basal ganglia and dorsal raphe nuclei in individuals with BPD and other severe mood disorders compared with controls (Manji *et al*,

2003). It is not currently known whether these alterations constitute developmental abnormalities conferring vulnerability to severe mood episodes, compensatory changes to other pathogenic processes, or the sequelae of recurrent affective episodes. However, a recent report showed that individuals at high risk for developing mood disorders exhibited reduced subgenual prefrontal cortical volumes, raising the possibility that this endophenotype may constitute a heritable vulnerability factor in these patients (Drevets *et al*, 2004). Overall, the reviewed data clearly show that BPD, undoubtedly a neurochemical illness, is also a disorder associated with impairments of cellular plasticity.

Magnetic resonance spectroscopy (MRS) has increasingly been used in the study of neuropsychiatric disorders. *N*-Acetyl-aspartate (NAA) is a predominant neurochemical compound that can be quantitatively assessed by MRS of the human brain. Pertinent to the present discussion is the fact that NAA is localized to mature neurons and synthesized within mitochondria. Interestingly, inhibitors of the mitochondrial respiratory chain decrease NAA concentrations, effects that correlate with reductions in ATP and oxygen consumption (Bates *et al*, 1996).

In BPD, decreased levels of NAA have been found in limbic and frontal cortex; these NAA reductions have been described (i) in hippocampus independent of mood state (Bertolino *et al*, 2003); (ii) in euthymic and medicated familial BPD I patients (Deicken *et al*, 2003); (iii) in the dorsolateral prefrontal cortex of euthymic and unmedicated adult BPD I and II patients (Winsberg *et al*, 2000); (iv) in orbitofrontal cortex of manic/mixed patients (Cecil *et al*, 2002); and (v) in dorsolateral prefrontal cortex of juvenile BPD patients (Chang *et al*, 2003). In addition, increased choline/NAA ratios were also found in the basal ganglia in both the depressive and euthymic states (Hamakawa *et al*, 1998). As discussed above, these findings may be the expression of underlying changes in ATP expenditure and availability, oxygen consumption, and/or glutamatergic activity in BPD. Similar changes in NAA have also been described in schizophrenia (mainly in prefrontal cortex) (Pae *et al*, 2004; Rowland *et al*, 2001; Theberge *et al*, 2004), indicating that some common pathophysiological mechanisms (either as cause or sequelae), may be present in these conditions. However, follow-up studies observing NAA changes after mood stabilizer treatment (described below) may indicate the particular relevance of this metabolite variation in BPD.

Furthermore, although there is some overlap in the MRS results between unipolar depression and BPD, higher specificity has been reported among bipolar populations. Decreased phosphocreatine levels and decreased baseline levels of beta- and total-nucleoside triphosphate have been reported in unipolar depressed subjects (reviewed by Iosifescu and Renshaw, 2003). In addition, Phosphorous-31 magnetic resonance spectroscopy (^{31}P MRS) studies that permit the determination of high energy phosphate metabolism inside the brain have reported normal (Kato *et al*, 1992) and decreased (Volz *et al*, 1998) phosphomonoester levels in subjects with unipolar depression compared with controls. Interestingly, independent literature reviews have also suggested that unipolar depression and BPD may possess different pathophysiological bases due to the different direction of the changes reported in H-MRS studies (Yildiz-Yesiloglu and Ankerst, 2006). In fact, a significant role for the phosphoinositol cycle/myoinositol was reported in the pathophysiology of BPD, whereas there was less evidence for a similar role in any other psychiatric condition (Kim *et al*, 2005).

Additional ^{31}P MRS studies have shown a decrease in phosphocreatine (PCr) and/or ATP levels in patients with BPD, and in one report that studied medicated patients with unipolar depression (Deicken *et al*, 1995; Kato *et al*, 1995; Volz *et al*, 1998). Kato and co-workers have conducted the most extensive series of studies investigating possible abnormalities in brain energy regulation in mood disorders. Consistent with the decreased PCr and ATP levels discussed above, this research group has also found low pH levels in patients with BPD compared with normal controls in the frontal cortex, in basal ganglia, and in the whole brain (Hamakawa *et al*, 2004; Kato *et al*, 1998, 2003). Indeed, these observations were among the first to lead to the postulation that BPD may be associated with mitochondrial dysfunction.

Findings of both decreased pH and increased lactate in BPD led to the very recent proposal that BPD subjects exhibit a shift away from oxidative phosphorylation towards glycolysis, thus reducing efficiency and total energy output (Stork and Renshaw, 2005). This suggests that impairment in mitochondrial functioning, which is normally responsible for the oxidative phosphorylation process, might cause the shift changes observed in BPD. In addition, if the respiratory chain of cellular metabolism were less available, the energy production would be displaced towards anaerobic glycolysis, consequently increasing lactate production (Stork and Renshaw, 2005). Notably, mitochondrial dysfunction is associated with reduced pH and increases in lactate. Thus, the seemingly distinct neuroimaging findings in BPD (reduced pH, increased lactate, reduced high energy phosphates, reduced NAA, and regional volumetric reductions) may all be linked by mitochondrial dysfunction as the more proximal cause (Stork and Renshaw, 2005).

ABNORMAL GENE EXPRESSION OF KEY MITOCHONDRIAL PROTEINS IN BPD

Additional evidence of dysregulated mitochondrial processes in BPD comes from an elegant series of postmortem brain microarray studies by Konradi *et al* (2004) (Table 3). They used gene arrays to analyze 12 558 nuclear genes in hippocampi from three different groups (healthy controls, BPD patients, and schizophrenia patients). Employing stringent statistical analyses, they found that the expression of only 43 genes was decreased in BPD compared with schizophrenia. Notably, 42% of the genes that were reduced in BPD brains coded for mitochondrial proteins and are involved in regulating oxidative phosphorylation in the mitochondrial inner membrane (including subunits of complexes I (NADH dehydrogenase in one gene), IV (cytochrome c oxidase in one gene), and V (ATP synthase in five genes) (Konradi *et al*, 2004)). These findings, as well as observations of decreased expression of the enzyme glutamic acid decarboxylase 67 and somatostatin (Heckers *et al*, 2002), indicate abnormal functioning of a subset of hippocampal interneurons in BPD; the possibility that dysfunction of these hippocampal interneurons involves

Table 3 Abnormal Post-Mortem Gene Expression of Key Mitochondrial Proteins in Subjects with Bipolar Disorder

Study subjects and methods	Principal finding	Gene array results	Authors' Remarks
10 HC/9 BPD/8 SZ Microarrays to study messenger RNA levels in hippocampus Verification of selected gene targets with quantitative RT-PCR	Significantly decreased mRNAs coding for mitochondrial proteins in hippocampus in BPD, but not in SZ. Extensive decrease in the expression of genes regulating oxidative phosphorylation and the adenosine triphosphate-dependent process of protesome degradation.	Expression levels of 42 genes decreased in BPD, and none in SZ. From those, 18 genes (42%) coded for mitochondrial proteins, including the subunits of: ETC complex I (nicotinamide adenine dinucleotide dehydrogenase in one gene) ETC complex IV (cytochrome c oxidase in one gene) ETC complex V (ATP synthase in five genes).	Konradi *et al*, 2004 The expression of genes coding for the enzymatic complexes governing oxidative phosphorylation is decreased in BPD. The ATP-dependent process of proteasome degradation is downregulated at the level of gene expression. Decreased pH and high-energy phosphate levels in BPD might be the result of mitochondrial dysfunction
10 HC/9 BPD/8 SZ SZ *Post hoc* analysis of an extant gene expression profiling database for hippocampus. Verification of selected gene targets with quantitative RT-PCR	Marked upregulation of 19 out of 44 apoptosis genes in BPD. Downregulation of genes associated with apoptotic injury and death in SZ. Marked downregulation of antioxidant genes in BPD, suggesting that accumulation of free radicals might occur in the setting of a previously reported decrease of the electron transport chain in this disorder.	Changes were observed in 24 out of a total of 44 genes in the apoptosis pathways in BPD. Apoptosis-related genes with the expression levels changed include: Key proapoptotic factors, such as JNKK, JNK were found to be downregulated. Several upregulated proapoptotic genes, including FAS ligand, FAS receptor, perforin, TNFa, c-Jun, c-myc, BAK, APAF-1, and caspases 2 and 8. Genes thought to inhibit apoptosis, such as TRAF1, IKK, IAP3, NF-kB, and bcl-2, showed increased expression in the BPD group DNA repair enzyme PARP showed a decrease in regulation. Primary or secondary detoxification of ROS-related genes with expression levels changed in BPD. Glutathione peroxidase 4, glyoxylase, esterase D-formylglutathione hydrolase, glutathione synthetase, glutathione S-transferase (the three, A2, M5, and omega, isoforms), catalase, and superoxide dismutase. Neuronal nitric oxide synthase (NOS1) was upregulated.	Benes *et al*, 2006 Fundamental differences in the gene expression regulation of apoptosis and antioxidant genes may help distinguish between the pathophysiology of BPD and SZ
8 HC/11 BPD Microarray analysis was based on a genechip with 19 000 human genes and universal human reference RNAs Verification of selected gene targets with quantitative RT-PCR	Gene candidates in three major functional pathways were differentially expressed in BPD, including genes in the mitochondrial electron transport chain, the phosphatidylinositol signaling system, and glycolysis/gluconeogenesis. Increased expression of the NADH-ubiquinone oxidoreductase 20-kDa subunit was found in BPD subjects receiving lithium at the time of death (compared with non-lithium-treated BPD subjects).	A total of 831 genes were differentially expressed in BPD. Eight downregulated genes were components of the ETC: ETC complex I; *NDUFS7* (NADH-ubiquinone oxidoreductase 20-kDa subunit), *NDUFS8* (NADH-ubiquinone oxidoreductase 23-kDa subunit) ETC complex III; *UQCRC2* (ubiquinol-cytochrome C reductase complex core protein 2) ETC complex IV; *COX5A* (cytochrome c oxidase polypeptide Va), COX6C (cytochrome c oxidase polypeptide Vic), *ATP5C1* (ATP synthase gamma chain) ETC complex V; *ATP5J* (ATP synthase coupling factor 6) and *ATP5G3* (ATP synthase lipid-binding protein) Five genes are involved in the phosphatidylinositol signaling system Four genes are involved in the process of glycolysis and gluconeogenesis	Sun *et al*, 2006 Considering that mitochondrial ETC is a major source for the generation of ROS, these findings suggest that oxidative damage may play an important role in the pathophysiology of BPD and that neuroprotection against this damage may be involved in the effect of lithium treatment

Abbreviations: HC, healthy controls; BPD, bipolar disorder subjects; SZ, schizophrenia subjects; RT-PCR, real-time polymerase chain reaction; ETC, mitochondrial electron transport chain; ATP, adenosine triphosphate.

abnormal mitochondrial energy metabolism is an intriguing hypothesis. Benes *et al* (2006) recently showed a marked downregulation of antioxidant genes in BPD (Table 3). These authors suggested that accumulation of free radicals might then occur in the setting of a previously reported decrease of the electron transport chain. In addition, a large number of apoptotic genes were reported to be upregulated in the hippocampus of BPD subjects (Benes *et al*, 2006).

Exciting findings pointing in this direction were also reported by Young and co-workers (Sun *et al*, 2006; Table 3). They showed that genes differentially expressed in subjects with BPD included genes in the mitochondrial electron transport chain. These genes included those responsible for the downregulation of NADH-ubiquinone oxidoreductase (20- and 23-kDa subunits, complex I), cytochrome c oxidase polypeptides (complex IV), and ATP synthase lipid-binding protein and gamma chain (complex V), all confirmed by PCR. Notably, expression of the NADH-ubiquinone oxidoreductase subunit was increased in subjects with ongoing lithium treatment (Sun *et al*, 2006), which may play a role in lithium's neuroprotective action (discussed below).

In subjects with a history of alcohol abuse or dependence, changes in gene expression from temporal cortex encoding mitochondrial proteins, the ubiquitin system, and signal transduction have also been observed (Sokolov *et al*, 2003). Thus, caution is needed when interpreting the results of postmortem brain studies due to the numerous potentially confounding factors, including substance abuse/dependence (a comorbidity often seen in BPD subjects), antemortem medication history, postmortem interval, and cause of death. In this respect, it is important to note that the phosphorylation state of proteins is extremely sensitive to postmortem interval (Li *et al*, 2003), as are decreased tissue pH and increased RNA degradation (Catts *et al*, 2005). Observed changes in pH could be related to the disease, or to agonal factors (Li *et al*, 2004; Iwamoto *et al*, 2005), or be due to postmortem changes.

Whether reduced pH in the postmortem tissue itself may be due to mitochondrial dysfunction is currently an area of ongoing research. Recent work by Vawter *et al* (2006) speaks to this issue. The work carefully contrasted control brains with low versus high pH, showing that 28% of genes in mitochondrially related pathways meet criteria for differential expression. Among several interesting results, they confirmed the relevance of the agonal-pH state effect in postmortem brain studies involving mitochondrial gene expression. Notably, when these authors controlled for these factors, potential candidate genes emerged; these genes, confirmed by Q-PCR, included the NR4A1 (mitochondrial) and HSPA2 (apoptotic chaperone) genes (Vawter *et al*, 2006). Considering that in humans there is no control for several antemortem factors (including medication status), it is not surprising that post-mortem findings are not entirely consistent. Thus, it is possible that lower postmortem pH findings—due to agonal factors known to be related to lower RNA integrity—may explain the gene expression changes. This issue remains to be addressed in subsequent studies.

The postmortem brain findings described above receive additional, indirect support from a recent peripheral cell study that effectively demonstrated a deficient adaptation to an energy–stress paradigm on peripheral cells from BPD subjects (Naydenov *et al*, 2007). They showed that lymphocytes from BPD individuals, cultured in medium with glucose deprivation, downregulated nuclear transcripts for proteins of the electron transfer chain, whereas the opposite effect was observed in the control samples (Naydenov *et al*, 2007).

MITOCHONDRIAL DYSFUNCTION AND OTHER NEUROPSYCHIATRIC CONDITIONS

Alterations in mitochondrial function are likely to play a role in the pathophysiology of neurodegenerative conditions including Huntington's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS), and, possibly, schizophrenia. Of interest, results from postmortem studies in schizophrenia include changes in cytochrome c oxidase activity (complex IV) in several cortical areas and subcortical nucleus (Cavelier *et al*, 1995; Maurer *et al*, 2001; Prince *et al*, 1999), complexes I and III (Maurer *et al*, 2001), as well as mRNA and protein levels of complex I proteins (Karry *et al*, 2004). Other studies have confirmed changes in complex I (Ben-Shachar *et al*, 1999), but, conversely, not complex IV activity (Dror *et al*, 2002) in platelets from schizophrenic patients. However, this evidence should be interpreted with caution considering the reported effect of antipsychotic medications on mitochondrial function (Balijepalli *et al*, 1999; Modica-Napolitano *et al*, 2003).

In toto, the data for alterations in the oxidative phosphorylation in brains of patients with schizophrenia are not entirely consistent. However, it is possible that common mitochondrial dysfunction may underlie pathophysiological changes and phenotypic expression across a number of neuropsychiatric conditions, particularly schizophrenia and BPD; these observations are noteworthy because, although these are undoubtedly discrete illnesses, a growing body of evidence suggests genetic and pathophysiological overlap among them (DePaulo, 2004).

We now turn to a discussion of the converging evidence that mood stabilizers regulate mitochondrial function.

MOOD STABILIZERS EXERT MAJOR EFFECTS ON PROTEINS KNOWN TO REGULATE MITOCHONDRIAL FUNCTION

The possible involvement of bcl-2 in the pathophysiology and treatment of BPD initially arose from mRNA differential display studies that suggested that bcl-2 might represent a common target for the actions of both chronic lithium and VPA (Chen *et al*, 1999). Chronic treatment of rats with therapeutic doses of lithium and VPA doubled bcl-2 levels in the frontal cortex, an effect due primarily to a marked increase in the number of bcl-2 immunoreactive cells in layers II and III of the anterior cingulated cortex (Chen *et al*, 1999; Manji *et al*, 1999, 2000a). Interestingly, the importance of neurons in the anterior cingulate has recently been emphasized in neuroimaging studies of BPD, particularly because these areas provide connections with other cortical regions and are targets for subcortical input (Rajkowska, 2000). Chronic lithium was also found to markedly increase the number of bcl-2 immunoreactive cells in the dentate gyrus and striatum (Manji *et al*, 1999). Subsequent to these findings, lithium was shown to increase bcl-2 levels in C57BL/6 mice

(Chen and Chuang, 1999), in human neuroblastoma SH-SY5Y cells *in vitro* (Manji *et al*, 2000b) and in rat cerebellar granule cells *in vitro* (Chen and Chuang, 1999).

Overall, the data clearly show that chronic lithium robustly increases levels of the neuroprotective protein bcl-2 in areas of rodent frontal cortex, hippocampus, and striatum *in vivo*, and in cultured cells of both rodent and human neuronal origin *in vitro*. Furthermore, at least in cultured cell systems, lithium reduces levels of the proapoptotic protein p53. As demonstrated recently, repeated electroconvulsive shock also significantly increases precursor cell proliferation in the dentate gyrus of the adult monkey, an effect that appears to be due to increased expression of bcl-2 (Perera *et al*, 2007).

Another target of mood stabilizers that may be relevant to mitochondrial function is glycogen synthase kinase 3 (GSK-3), a constitutively active kinase that is known to inhibit the mitochondrial multiprotein complex pyruvate dehydrogenase (PDH) (Hoshi *et al*, 1996)—notably, lithium and possibly VPA are known to inhibit this kinase (Gould and Manji, 2002). PDH acts as a key linkage (and point of regulation) between glycolysis and the tricarboxylic acid cycle. Inhibition of GSK-3 by mood stabilizers may lead to disinhibition of PDH, thus to an increase in maximal metabolic rate, and a more adequate supply of ATP in tissues with high energy requirements, such as brain.

Recent data also suggest that the mitochondrion is likely one of the main sites of action of GSK-3. Although GSK-3 is present throughout the cell, analysis of subcellular fractions has shown that GSK-3 in nuclei and mitochondria has a higher level of basal activity (Bijur and Jope, 2003; Jope, 2003); these pools are selectively activated by proapoptotic stimuli. GSK-3 exerts proapoptotic neuronal effects by regulating mitochondrial localization of bax (Linseman *et al*, 2004), whereas GSK-3 inhibition has been shown to inhibit or delay activation of PTP (Juhaszova *et al*, 2004; Murphy, 2004). Thus, the observation that lithium exerts its inhibitory effects on GSK-3 within mitochondria is noteworthy (Bijur and Jope, 2003). In a complementary fashion, lithium and VPA may also modulate intracellular Ca^{2+} signaling (an effect probably associated with the antiapoptotic properties of these mood stabilizers) by suppressing the activational phosphorylation of the NR2B subunit of the NMDA receptor (Hashimoto *et al*, 2002). Consistent with these effects on major antiapoptotic proteins, several studies have now demonstrated that lithium and VPA attenuate the activation of pro-apoptotic cascades (Pan *et al*, 2005; Lai *et al*, 2006; Yeste *et al*, 2007; Chen *et al*, 2006; Shao *et al*, 2005; Cui *et al*, 2007).

Lithium exerts robust neuroprotective effects in preclinical paradigms

In view of its major effects on BDNF, bcl-2 and GSK-3, it is not surprising that recent studies have investigated lithium's potential neuroprotective effects in a variety of preclinical paradigms, demonstrating robust neuroprotective properties against a variety of insults (reviewed by Bachmann *et al*, 2005; Chuang and Priller, 2006; Manji *et al*, 2000a; Schloesser *et al*, 2007).

Notably, lithium pretreatment has been demonstrated to protect cultured brain neurons from glutamate-induced, NMDA receptor-mediated apoptosis (reviewed by (Chuang and Priller, 2006). Excessive NMDA throughput is likely involved in stress-induced hippocampal atrophy, and has been implicated in the pathogenesis of a variety of neurodegenerative diseases such as stroke, Huntington's disease, ALS, spinal cord injury, brain trauma, and cerebellar degeneration. In cultured neurons, lithium-induced neuroprotection against glutamate excitotoxicity occurs within the therapeutic concentration range of this drug and requires 5–6 days of pretreatment for maximal effects. The lithium neuroprotection requires BDNF induction and activation of its receptor TrkB, and is associated with upregulation of bcl-2, downregulation of the proapoptotic proteins p53 and Bax, and inhibition of caspase-3. Treatment of cultured neurons with other GSK-3 inhibitors or transfection with GSK-3 siRNA mimics the neuroprotective effects of lithium (Liang and Chuang, 2007), again suggesting a critical role of GSK-3 in mediating neuroprotection.

Lithium also shows beneficial effects in a number of animal models of neurodegenerative diseases. For example, pre- or post-insult treatment with lithium suppresses cerebral ischemia-induced brain infarction, caspase-3 activation, and neurological deficits in rats, and these neuroprotective effects are associated with induction of heat shock protein 70 and decreased expression of Bax (Ren *et al*, 2003; Xu *et al*, 2003). Several independent studies demonstrated that lithium has neuroprotective effects in animal and cellular models of Alzheimer's disease, Huntington's disease, Parkinson's disease, retinal degeneration, spinal cord injury, and HIV infection (reviewed by (Chuang and Priller, 2006). Notably, Phiel *et al* (2003) demonstrated that therapeutic concentrations of lithium, by acting on GSK-3, blocked the production of Aβ peptides by interfering with amyloid peptide precursor protein (APP) cleavage at the γ-secretase step. Importantly, lithium also blocked the accumulation of Aβ peptides in the brains of mice that overproduce APP.

Similarly, lithium administration has been shown to significantly lower levels of phosphorylation at several epitopes of tau known to be hyperphosphorylated in Alzheimer's disease and to significantly reduce levels of aggregated, insoluble tau (Noble *et al*, 2005). Furthermore, levels of aggregated tau correlated strongly with degree of axonal degeneration, and lithium-treated mice showed less degeneration if administration was started during early stages of tangle development. Most recently, it has been demonstrated that lithium is neuroprotective in APP transgenic mice (Rockenstein *et al*, 2007). Thus, mice treated with lithium exhibited improved performance in the water maze, preservation of the dendritic structure in the frontal cortex and hippocampus, and decreased tau phosphorylation (Rockenstein *et al*, 2007). Chronic lithium treatment also protects against neurodegeneration and improves spatial learning deficits in rats perfused with Aβ fibrils (de Ferrari *et al*, 2003).

HUMAN EVIDENCE SUPPORTING THE NEUROTROPHIC EFFECTS OF MOOD STABILIZERS

Almost a decade ago, volumetric MRI studies demonstrated that familial BPD patients had approximately 40% lower

gray matter volumes in the left subgenual prefrontal cortex; a subsequent re-analysis of these data showed that patients treated with chronic lithium or VPA did not exhibit the subgenual prefrontal cortex volumetric reduction (discussed by Gould *et al*, 2004; Quiroz *et al*, 2004).

To examine potential neurotrophic effects of lithium more directly, several longitudinal studies have recently been undertaken. Chronic lithium administration at therapeutic doses was found to increase NAA concentrations in the human brain *in vivo* (Moore *et al*, 2000); furthermore, a correlation of approximately 0.97 between lithium-induced NAA increases and regional voxel gray matter content was observed. Interestingly, the region-specific bcl-2 increases induced by lithium in rodent brain cortices (eg, gray versus white matter) colocalize with the aforementioned areas. In follow-up studies, it was hypothesized that lithium-induced mitochondrially-mediated trophic effects would lead to neuropil increases and consequently to increased brain gray matter volume in BPD patients. Thus, gray matter volumes were quantified at baseline and then repeated after 4 weeks of lithium at therapeutic doses (Moore *et al*, 2000). Chronic lithium was found to significantly increase total gray matter content; no significant changes were observed in brain white matter volume or in quantitative measures of the regional cerebral water content, thereby providing evidence that the observed increases in gray matter content were due to neurotrophic effects as opposed to any possible cell swelling and/or osmotic effects associated with lithium treatment (Moore *et al*, 2000). In addition, several independent cross-sectional studies have now demonstrated that lithium-treated patients with BPD show increased gray matter volumes compared to untreated BPD patients (Sassi *et al*, 2002, 2004; Chang *et al*, 2005; Bearden *et al*, 2007).

Most recently, another study was undertaken in well-characterized BPD-depressed subjects ($n = 28$) at baseline (medication free), and following chronic lithium administration (4 weeks) (Moore *et al*, 2005). Significant increases in total gray matter volume were observed in BPD subjects following chronic lithium administration, confirming the previous preliminary study. Moreover, only responders showed increases in gray matter in the left subgenual prefrontal cortex (Moore *et al*, 2005). These data suggest that lithium—likely through its effect on mitochondrial functioning—produces a reversal of illness-related atrophy. These findings may have implications not only for long-term functional outcome, but also for 'here and now' symptom resolution.

CONCLUDING REMARKS

We have outlined here the evidence supporting the contention that mitochondrial function is integral to many facets of BPD. Mitochondria are intracellular organelles best known for their critical roles in regulating energy production through oxidative phosphorylation, regulation of Ca^{2+}, and as critical mediators of cellular apoptosis. However, increasing evidence suggests that mitochondria may be integrally involved in the general processes of synaptic plasticity. Indeed, increased synaptic activity has been shown to induce the expression of mitochondrially encoded genes, suggesting that the regulation of metabolism is an important component in the long-term regulation of synaptic strength. These findings suggest that mitochondrial Ca^{2+} sequestration plays a key role in modulating the tone of synaptic plasticity in a variety of neuroanatomical circuitry and regions mediating complex behaviors, including those implicated in the pathophysiology of mood disorders.

It needs to be reiterated that although some studies suggest a parent-of-origin effect, we are not implying that BPD is a classic mitochondrial disorder, but rather that many upstream abnormalities (likely nuclear genome coded) converge to regulate mitochondrial function implicated both in abnormalities of neurotransmitter synaptic plasticity and long-term cellular resilience.

Hovatta *et al* (2005) recently used a combination of behavioral analysis and quantitative gene expression profiling of several brain regions in six inbred mouse strains. They found that genes involved in oxidative stress metabolism were related to complex affective behaviors. Together, these results suggest that the mitochondria-mediated impairments of plasticity observed in BPD may have ramifications not only for long-term disease progression/course of illness/functional impairments, but also for BPD symptomatology. Indeed, as previously mentioned, it has recently been demonstrated that short-term lithium-induced increases in subgenual prefrontal cortex gray matter were related to treatment response (Moore *et al*, 2005).

There has, unfortunately, been little progress in developing truly novel drugs specifically for the treatment of BPD, and most recent additions to the pharmacopeia are brain-penetrant medications developed for the general treatment of epilepsy or schizophrenia. Here, we have outlined evidence—derived from neuroimaging, postmortem brain, biochemical, and pharmacological studies—to support the contention that mitochondrial function is integral to many facets of BPD. These observations raise the intriguing possibility that enhancing mitochondrial vigor may represent an important adjunctive strategy for the optimal long-term treatment of BPD. Novel molecular targets to improve mitochondrial function include pharmacological attempts to bypass defects in the respiratory chain, scavenging excessive oxygen radicals (reviewed by Dimauro *et al*, 2004), and enhancers of mitochondrial membrane stabilization, including, theoretically, inhibitors of PTP. These developments hold much promise for the discovery of new therapeutics for this devastating illness.

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DISCLOSURE/CONFLICT OF INTEREST

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