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Understanding the neurobiology of bipolar depression

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Abstract

Many studies have shown decreased brain volume and cell number in prefrontal and limbic regions of bipolar disorder subjects, suggesting presence of disturbed neuronal circuitry and impaired neuroplasticity in these regions. The serotonin system plays an important role in depression and is a target of antidepressants. Studies have shown that the major serotonin metabolite 5-HIAA and serotonin transporter activity are decreased in cerebrospinal fluid, brain or platelets of subjects with bipolar depression, indicating that an abnormal serotonin system also contributes significantly to this disease. Mitochondria regulate synthesis, release and uptake of neurotransmitters via energy production. Evidence has shown that glucose metabolic rate and cerebral blood flow are decreased in bipolar depression. Studies also suggest defects in mitochondrial electron transport chain and oxidative damage in bipolar disorder. These studies together indicate that bipolar depression may be associated with an abnormal serotonin system resulting from mitochondrial dysfunction-induced impaired neuroplasticity in neuronal circuitry related to mood regulation.

Introduction

The depressed phase of bipolar disorder remains an enormous challenge for patients, their families and to clinicians. Depression is far more common in bipolar disorder than is mania, and is associated with high rates of suicide or suicide attempts and marked impairment in function [1–5]. There has long been debate about whether bipolar depression is similar to or different from unipolar depression, with recognition of different treatment responses and clinical courses suggesting a different neurobiology.

Mood stabilizing drugs are useful for treatment of different phases of the illness including treatment of mania and depression acutely and prophylaxis against relapse into either state. There is a general consensus that treating either acute depression or preventing relapses into depression is more challenging than treating mania and that the drugs we use to treat the disorder are less effective for these symptoms [6]. Therefore, a better understanding of the molecular mechanism of bipolar disorder, and particularly of bipolar depression, is critical to improving treatment for the disease.

Many studies using brain imaging and postmortem brain tissue have revealed reduced brain volume and cell density in prefrontal cortex and limbic regions from subjects with bipolar disorder. These findings suggest that critical neuronal circuits made up of regions that modulate emotion and mood are disturbed, which subsequently affects synthesis, release, reuptake and other functions of neurotransmitters and results in impairment of neuroplasticity. Serotoninergic neurotransmitter system has been extensively studied in the pathology of major depressive disorder, and is targeted by antidepressants. Studies also implicate the serotoninergic system in bipolar depression and as a target for many mood stabilizing drugs, suggesting that the system may also have a critical role in the pathology of bipolar disorder. It remains to be determined what causes or promotes the loss in neuroplasticity and cell loss in bipolar disorder. Among several plausible hypotheses, the possibility that altered energy metabolism and oxidative stress occurs in the illness lead to cellular damage is becoming increasing accepted. Mitochondria are enriched in both dendrites and synaptic terminals, produce energy for many neuronal functions including synthesis, release and reuptake of neurotransmitters, and are important in regulation of neuronal plasticity and surviving. Increasing evidence suggest impaired energy metabolism and mitochondrial dysfunction in brain of bipolar disorder patients.

In the following chapter, we review findings on the neurobiology of depression. Most studies in bipolar disorder have not focused only on the depressed phase of illness but have looked at patients in all phases of illness. There is a long debate about whether these may be a specific neurobiology of depression in bipolar disorder and how it relates to unipolar depression. We have focused on the three areas described above as they are related to approaches that have been successful in the study of major depression. We suggest in this review that cell loss and decreased neuroplasticity occurred in key limbic and cortical regions lead to monoaminergic dysfunction including the serotonin system, which could contribute to depressive symptoms. Finally we suggest that altered energy metabolism occurs in bipolar disorder which ultimately results in cell damage and altered neurotransmission.

Structural abnormality in frontal and limbic brain regions of subjects with bipolar disorder

Mood regulation appears to be related to activity in the prefrontal cortex and anterior cingulate cortex, and in the hippocampal and amygdalar limbic brain regions, all of which together regulate behaviors such as emotion, attention, motivation and cognition. Prefrontal cortex plays a critical role in thought processes that control mood, cognition and motor behavior functions. Anterior cingulate cortex is important to attentional, emotional and cognitive mental functions, and in the initiation of motivated behavior. Hippocampal and amygdalar limbic regions are involved in production of emotion, in motivation, and

in emotional association with memory [7–10]. In patients with bipolar disorder, compelling evidence for structural abnormalities, cell loss and reduced cell density in these key brain regions associated with mood regulation has been provided by neuroimaging and postmortem brain studies.

Using magnetic resonance imaging, a number of these studies have found a decrease in grey matter volume in prefrontal cortex from bipolar and unipolar depression patients (Fig. 1) [11–14]. However, the findings for changes in hippocampal and amygdalar volume in adult bipolar subjects are equivocal compared to those for prefrontal cortex [15–21]. The reasons for the discrepant data for structural hippocampal and amygdalar changes may reflect the varied histories of illness diagnosis and treatment that are characteristic of adult bipolar disorder populations. On the other hand, recent studies in children and adolescents with bipolar disorder have consistently reported decreased amygdalar volume [22–25]. Altshuler et al. [26] found that amygdalar volume in bipolar disorder subjects with a history of psychoses was positively correlated with the number of manic episodes, indicating that course of illness may play a role in exacerbating volumetric changes.

Postmortem brain studies have provided direct evidence suggesting that reduced cell number and cell density may contribute to structural changes in the brain that have been observed in bipolar disorder subjects. Rajkowska et al.

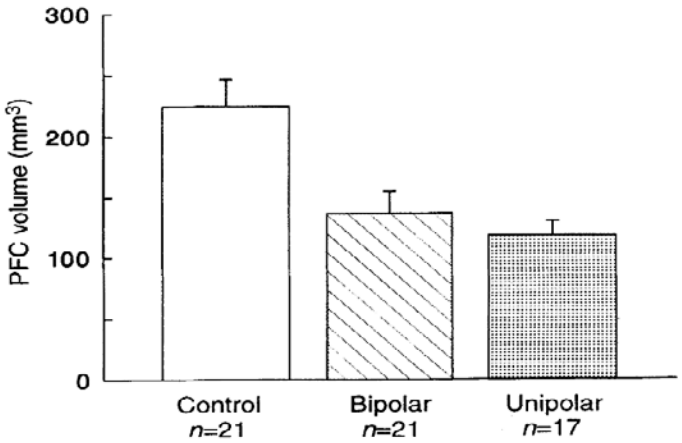

Figure 1. MRI-based volumes of the left subgenual prefrontal cortex (PFC) grey matter differed between the bipolar disordered, unipolar depressed and control groups (ANOVA, $F = 9.8$; $P < 0.0002$, co-varying for gender, age and whole brain volume). *Post hoc* tests (Tukey-Kramer) showed significant volumetric decreases in the bipolar and unipolar groups relative to the control group. Whole-brain MRI volume and skull X-ray measures (product of anterior-posterior distance between the inner tables of the skull at the estimated bicommissural segment and perpendicular distance from the midpoint of the bicommissural segment to the vertex) were slightly smaller in the unipolar group compared with the bipolar and control groups, and did not differ between the bipolar and control groups. The left subgenual PFC/whole brain volume ratio was also reduced in the bipolar and unipolar groups, being $1.8 \times 10^{-4} \pm 0.74 \times 10^{-4}$, $1.1 \times 10^{-4} \pm 0.64 \times 10^{-4}$, and $1.1 \times 10^{-4} \pm 0.51 \times 10^{-4}$ in the control, bipolar, and unipolar groups, respectively ($F = 8.4$; $P < 0.001$) [11].

[27] found, in the prefrontal area, that pyramidal cell density in layers III and V were decreased in bipolar disorder subjects. Non-pyramidal neurons were also reported to be decreased in layer II of anterior cingulate cortex and in the CA2 region of hippocampus [28, 29]. Recent data have also indicated decreased neuronal size and number in the lateral nucleus of the amygdala in subjects with bipolar disorder [30, 31]. Aberrant mossy fiber sprouting has been observed in the hippocampus of bipolar disorder subjects [32], which is suggestive of altered neuroplasticity. Levels of the neuronal viability marker N-acetyl-aspartate was shown to be decreased in *post mortem* prefrontal cortex of bipolar disorder subjects [33, 34]. Glial number and density were also reduced in the same region [27, 35]. The glial fibrillary acidic protein isoforms were found to be decreased in the prefrontal cortex of both bipolar disorder and unipolar depression subjects, suggesting decreased astrocytes [36]. It has also been reported that dystrophic alterations and reduced density occur in oligodendroglial cells in layer VI of BA 9/10 in bipolar disorder subjects [37–39]. These results suggest that both astrocytes and oligodendroglial cells are involved in the changes observed in glial cells.

Changes of volume and cell density in prefrontal and limbic brain regions suggest a possible disruption of neuronal circuits which regulate mood and emotion. Brain derived neurotrophic factor (BDNF) is abundantly and widely distributed in brain. It regulates synapse formation, differentiation and neuronal survival, and plays an important role in regulation of neuroplasticity and behaviors. Recent studies have shown that altered expression of BDNF occurs in brain in bipolar disorder, suggesting that it is an important factor in causing or promoting changes in neuronal structure or density in these brain regions. For example, it has been reported that levels of BDNF protein were lower in postmortem hippocampus of subjects with bipolar disorder than controls [40]. The val66met BDNF polymorphism has also shown to be associated with bipolar disorder [41–44]. Recently, a number of studies also found abnormal expression of BDNF in peripheral blood from bipolar patients. Cunha et al. [45] investigated serum BDNF levels in manic, depressive and euthymic states of BD patients and found that serum BDNF levels in manic and depressive states, but not in euthymic state, were decreased when compared with healthy controls. Decreased serum BDNF levels have also been found in euthymic patients with bipolar disorder, and depressed and euthymic patients with unipolar depression [46]. Our laboratory also found that BDNF levels were significantly lower in lymphoblasts from bipolar disorder subjects when compared with matched healthy controls [47] (Fig. 2). These findings together implicate BDNF may be one of the critical factors which ultimately contribute to a loss of neuroplasticity and cell loss in bipolar disorder.

There are many consequences to disruption of these neurons and impairment of neuroplasticity, one of which is the possibility that these changes may lead to a predisposition for depressive and manic affective responses. The serotoninergic system has long been identified as important in mood and in particular depression. Indeed, as reviewed below both older and very recent data

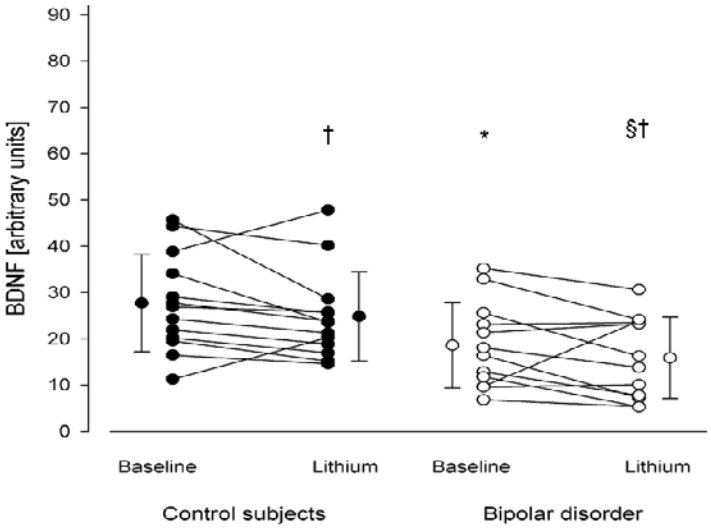

Figure 2. BDNF protein levels in transformed lymphoblasts from non-psychiatric controls and lithium-responsive bipolar subjects, with and without 1 mM lithium treatment for 7 days, and unaffected relatives. BDNF protein levels were 36% lower in subjects with bipolar disorder compared to non-psychiatric controls (*, $p = 0.02$), and this decrease remained (33%, §, $p = 0.02$) after lithium treatment. Lithium treatment decreased BDNF levels in both bipolar and control populations (†, $p = 0.05$). All measures are expressed as mean ± standard deviation [47].

suggest the importance of this same neurotransmitter in bipolar depression. We speculate that this may be one of the consequences of the cellular changes in brain of patients with bipolar disorder which is critical to the development of depressive symptoms and episodes.

Serotonin neurotransmitter system in subjects with bipolar depression

The serotonergic neurons project to many cortical brain regions and regulate many brain functions such as emotion, cognition, motor function, pain sensitivity and many others. Based upon evidence from neuroimaging, postmortem brain, peripheral blood cell, pharmacological and genetic studies, an abnormal serotoninergic system is well acknowledged to play an important role in the pathophysiology of unipolar depression. Although whether molecular and cellular mechanisms are distinct in unipolar depression and bipolar depression remains unclear, a number of studies have also suggested that the serotoninergic system, particularly serotonin level and serotonin transporter reuptake activity, is altered in bipolar depression.

Studies have shown that the turnover of serotonin is altered in bipolar depression. 5-hydroxyindoleacetic acid (5-HIAA) is the main metabolite of serotonin. Decreased concentrations of this serotonin metabolite have been

consistently reported in cerebrospinal fluid of bipolar depressed patients. It has been reported that the concentration of 5-HIAA in cerebrospinal fluid of depressed subjects, including both bipolar and unipolar subjects, was significantly lower than that of healthy controls [48]. The concentration of 5-HIAA in cerebrospinal fluid has also been found to be decreased in bipolar depression subjects with suicide attempts when compared with controls [49]. It is interesting that 5-HIAA levels of cerebrospinal fluid were significantly increased in female manic patients when compared with gender matched controls [50]. Decreased 5-HIAA levels in depression, and increased 5-HIAA levels in mania, suggest an important relevance of 5-HIAA in manic and depressive symptoms of bipolar disorder. In order to determine if monoamine metabolites are critical to lethality of suicide attempts in bipolar patients, Sher et al. [51] recently using high-performance liquid chromatography to analyze the relationship between 5-HIAA, dopamine metabolite homovanillic acid (HVA) and norepinephrine metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG) levels in cerebrospinal fluid, and maximum lethality of suicide attempts during a 2-year follow up in 27 bipolar depressed patients. They found that 5-HIAA, HVA, and MHPG levels were negatively correlated with the maximum lethality of suicide attempts during this follow-up period. Decreased levels of monoamine metabolites have also been found in postmortem brain tissue in subjects with bipolar depression. Young et al. [52] found that in bipolar disorder subjects who died while depressed, 5-HIAA levels were decreased in postmortem frontal and parietal cortex, and 5-HIAA/serotonin ratio was decreased in postmortem temporal cortex, while HVA levels were decreased in postmortem parietal cortex and HVA/dopamine ratios were decreased in postmortem occipital cortex when compared with controls. These studies suggest that decreased production or increased removal of 5-HIAA in cerebrospinal fluid and brain play an important role in bipolar depression, and also suggest that levels of monoamine metabolites may be used as predictors of lethality of suicide attempts in subjects with bipolar disorder.

Serotonin transporter in presynaptic terminals reuptakes the neurotransmitter serotonin from synaptic cleft into presynaptic neurons, and is a key molecule for control of synaptic serotonin levels. Serotonin transporter is also primary target for many antidepressants [53, 54]. A number of studies indicate abnormal serotonin transporter activity in subjects with bipolar depression. Among these studies, most reported that the serotonin transporter activity is decreased in this disorder, but some also reported that the serotonin transporter activity is not changed or increased.

Serotonin transporter activity has been measured by analyzing the binding of selective serotonin reuptake inhibitor with the transporter uptake site. Leake et al. [55] studied 15 subjects with depression, 9 with major depressive disorder and 6 with bipolar disorder, and found that the concentration of ^{3}H-citalopram binding to serotonin transporter was lower in postmortem frontal cortex from depressed subjects when compared with controls. They also found that serotonin uptake sites were attenuated in a trend in subjects with bipolar

depression. Human platelets are able to uptake serotonin and resemble presynaptic serotoninergic neurons [56], which provide a convenient model to investigate involvement of the serotonin system in the pathophysiology of mood disorders. Stahl et al. [57] found that serotonin uptake was significantly reduced in subjects with bipolar depression, but not in subjects with schizophrenia when compared to controls. It has also been found that the maximum rate for serotonin reuptake into platelets was reduced in subjects with bipolar depression and unipolar depression [58–60]. However, serotonin transporter activity in platelets has also been reported to be no change between subjects with controls and bipolar depression [61]. Although no difference of serotonin transporter activity between subjects with depression and healthy controls has also been found, serotonin transporter activity has been found to be significantly lower in subjects with bipolar depression than unipolar depression [62]. A difference in this transporter activity between subjects with bipolar depression and unipolar depression may be useful to classify clinically defined subtypes of depression in affective disorders.

Decreased serotonin transporter activity in bipolar depression was also confirmed by a study using positron emission tomography. Oquendo et al. [63] recently studied brain serotonin transporter binding using positron emission tomography and radiolabeled *trans*-1,2,3,5,6,10-β-hexahydro-6-[4-(methylthio) phenyl] pyrrolo-[2,1-a]-isoquinoline (^{11}C(+)-McN5652) in 18 medication-free patients with bipolar depression compared with 41 controls. They found that serotonin transporter binding activity was reduced by 16% to 26% in the midbrain, amygdala, hippocampus, thalamus, putamen, and anterior cingulate cortex of patients with bipolar depression (Fig. 3). Using the same technology, serotonin transporter binding activity has also been found to be decreased in subjects with unipolar depression [64–66]. Low serotonin transporter binding activity may represent serotonin transporter internalization that is facilitated by decreased serotonin levels in synaptic cleft in subjects with bipolar depression. Because serotonin transporter binding has been used as is a marker for serotoninergic neurons, low serotonin transporter binding activity may also indicate fewer serotoninergic neurons in subjects with bipolar depression [63, 67, 68]. [^{11}C]-3-amino-4-(2-dimethylaminomethyl-phenylsulfanyl)-benzonitrile ([^{11}C] DASB), a recently developed diphenyl sulfide radioligands, is able to higher selectively bind serotonin transporter *in vivo* than previously available radioligands. Cannon et al. [69, 70] analyzed the serotonin transporter binding potential in 18 unmedicated subjects with bipolar depression and 37 healthy controls using positron emission tomography and [^{11}C] DASB. They found that the serotonin binding activity was decreased in pontine raphe-nuclei of the brainstem, but increased in the thalamus, dorsal cingulate cortex, medial prefrontal cortex and insula when compared with controls. They also found that serotonin transporter binding was lower in the midbrain and higher in anterior cingulate cortex of bipolar subjects with a history of suicide attempts when compared to controls or bipolar subjects without suicide attempts. It is interesting that subjects with bipolar depression have shown lower serotonin transporter binding poten-

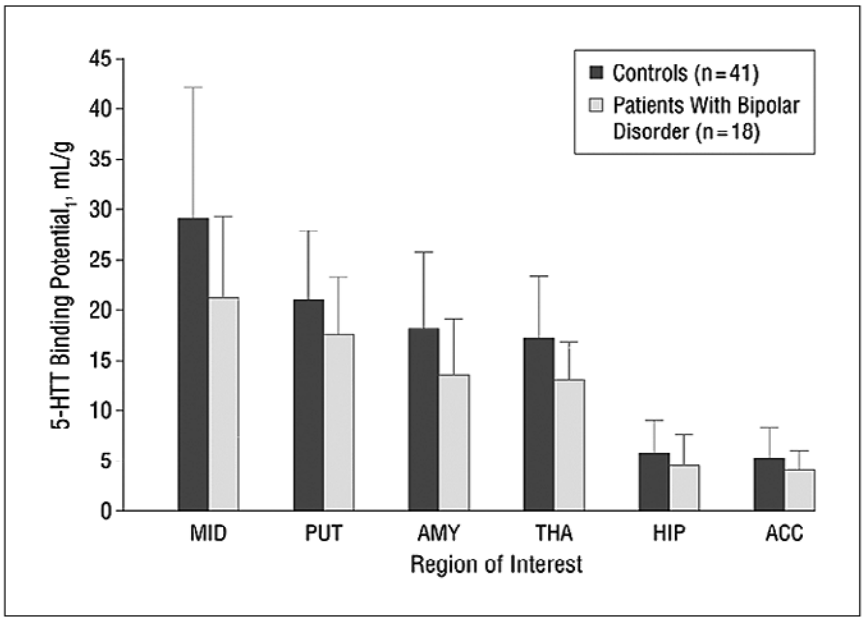

Figure 3. Lower radiolabeled trans-1,2,3,5,6,10-hexahydro-6-[4-(methylthio)-phenyl]pyrrolo-[2,1-a]-isoquinoline ([^{11}C](+)-McNeil 5652) binding potential (BP1) to the serotonin transporter (5-HTT) in nonmedicated patients with bipolar disorder in six regions of interest compared with controls ($F1,58 = 5.41$; $P = .02$). ACC indicates anterior cingulate cortex; AMY, amygdala; HIP, hippocampus; MID, midbrain; PUT, putamen; and THA, thalamus. Vertical bars represent the mean likelihood approach to the graphical method modeled BP1 (VT[region] – VT[cerebellum]) for each region; error bars, ±1 SD [63].

tial in pontine raphe-nuclei region than subjects with unipolar depression and controls, while subjects with unipolar depression have shown higher serotonin binding potential in periaqueductal gray of middle brain than subjects with bipolar and controls. This difference of serotonin binding potential in brainstem between unipolar depression and bipolar depression may be relevant to patterns of illness symptoms and pharmacological sensitivity for these disorders.

In summary, the levels of the major metabolite of serotonin 5-HIAA may be decreased in cerebrospinal fluid and brain of subjects with bipolar depression, suggesting that intra-synaptic serotonin levels are low in this disorder. The findings of serotonin transporter binding activity in bipolar depression however are inconsistent. Most studies have suggested that serotonin transporter binding activity is decreased in bipolar depression, while others have reported that serotonin transporter binding activity is increased. The inconsistency may result from small sample sizes, differing ligands, confounding medications, and differing reference tissues, among other reasons.

Serotonin reuptake appears to be dysregulated in bipolar depression quite similar to which is seen in unipolar depression [71]. Many studies suggest that

BDNF regulates the development and function of serotoninergic neurons [72–75]. Recent studies have also shown that administration of selective serotonin reuptake inhibitor antidepressants increase gene expression of BDNF [76–80]. As described above, decreased BDNF levels have also been shown in bipolar disorder. Since both serotoninergic system and BDNF play an important role in brain development via regulation of neurite outgrowth, synaptogenesis, and cell survival, dysregulation in serotoninergic system and BDNF imply impaired neuroplasticity in bipolar depression, resulting in the cell loss and damage found in brain imaging and *post mortem* brain studies.

Abnormal energy metabolism and dysfunctional mitochondria

While the factors that cause or promote cell loss and change in brain of patients with bipolar disorder, ultimately leading to altered neurotransmission, remain to be fully established, altered energy metabolism resulting in oxidative stress may be one important contributing factor. Mitochondria are enriched in both dendrites and synaptic terminals, and play important roles in neuroplasticity and cell viability via energy production. Therefore, abnormal regulation of serotonin system in bipolar depression may result from impaired neuroplasticity induced by abnormal energy metabolism and dysfunctional mitochondria.

Metabolic pathways for energy production in humans include glycolysis, the citric acid cycle and the electron transport chain. The primary source for energy production in the brain is glucose. During the glycolysis process, one molecule of glucose is converted into two molecules of pyruvate that are then used for making more molecules of ATP in the citric acid cycle and in the electron transport chain in mitochondria [81, 82]. A number of studies have indicated presence of impaired energy metabolism in bipolar depression. Baxter et al. [83] using positron emission tomography and fluorodeoxyglucose F18 in a small group of subjects (11 with unipolar depression, 5 with bipolar depression, 5 with mania, 3 with bipolar mixed states and 9 normal controls) found that subjects with bipolar depression have significant lower cerebral metabolic rates for glucose when compared with other groups. The ranking for glucose metabolic rates in the whole brain from low to high are bipolar depression, unipolar depression or a mixed state, manic state respectively. Later this research group [84] also analyzed cerebral glucose metabolism in a larger group of subjects with depression that included bipolar depression, unipolar depression and obsessive-compulsive disorder with secondary depression. They found that the glucose metabolic rate was significantly lower in subjects with bipolar depression and unipolar depression than in controls in the left dorsal anterolateral prefrontal cortex. The depressive subjects with medication showed increased glucose metabolic rates in this brain region, and the percentage of change was correlated with the Hamilton Rating Scale for Depression score. The rate of glucose metabolism was also found to be

decreased in the prefrontal cortex of subjects with familial bipolar depression and familial unipolar depression, but increased in subjects with mania [11]. However, it has been also reported that the rate of glucose metabolism was higher in subjects with either unipolar depression or bipolar depression than in healthy controls in the left amygdale [85]. These studies suggested that change of glucose metabolism represents changes in mood state, has brain regional difference and contributes a significant role in mood disorders. Glucose metabolic process in brain may also be targeted by pharmacological treatment.

Efficient cerebral blood flow is required to meet the brain's metabolic demands. Studies have shown lower cerebral blood flow in subjects with bipolar depression. Ito et al. [86] using ^{99m}Tc-hexamethylpropyleneamineoxime as a cerebral blood flow tracer for single photon emission computed tomography scan in 11 patients with unipolar depression, 6 patients with bipolar depression and 9 age-matched normal control subjects. They found that cerebral blood flow was significantly decreased in the prefrontal cortices, limbic systems and paralimbic areas of subjects with unipolar depression and bipolar depression, and there was no difference observed between these two types of depression. Using positron emission tomographic images, Drevets et al. [11] also found that cerebral blood flow was decreased in the prefrontal cortex of subjects with unipolar depression and bipolar depression. Rubin et al. [87] analyzed young adults in episodes of either acute mania or major depression. They found that cerebral blood flow was significantly lower in subjects with mania and depression than in controls in anterior cortical areas. In contrast to these studies, Tutus et al. [88] found that cerebral blood flow was decreased only in the left frontal lobe of subjects with unipolar depression but not bipolar depression when compared to subjects with and controls. Recently, Krüger et al. [89] found that cerebral blood flow was decreased in the orbitofrontal and inferior temporal cortices but increased in the dorsal/rostral anterior cingulate and anterior insula after induction of transient sadness in euthymic lithium responder bipolar patients and their healthy siblings. These findings suggest that energy metabolism is decreased in depressive mood states, but clear understanding of cerebral blood flow in bipolar depression requires further investigation.

Phosphorus-31 magnetic resonance spectroscopy allows detecting high-energy phosphates and the intracellular pH [90, 91]. Using this technology, Kato et al. [92, 93] found that subjects with bipolar disorder have shown increased phosphomonoester and intracellular pH in brain in the depressive mood state when compared with the euthymic state, while those values in the euthymic state were significantly lower as compared to age-matched normal controls. Increased phosphomonoester has also been found in the frontal lobe of subjects with unipolar depression when compared to age-matched controls. Phosphomonoester levels are correlated negatively with the degree of depression [94]. These studies suggest that disturbed phospholipid and intracellular high-energy phosphate metabolism may be common between bipolar depression and unipolar depression. Phosphocreatine is a high-energy compound

made from creatine and ATP. It has been found that phosphocreatine in brain was significantly decreased in subjects with Bipolar II in all hypomanic, euthymic and depressive states when compared to controls. Phosphocreatine was significantly lower in subjects with severe depression than subjects with mild depression [92, 95]. Further, the phosphocreatine levels were significantly lower in the left frontal lobe of subjects with bipolar depression than the normal controls, while phosphocreatine levels were lower in the right frontal lobe of the subjects in the manic and the euthymic states than controls. Phosphocreatine levels in subjects with bipolar depression were negatively correlated with the Hamilton Rating Scale for Depression score [96]. Decreased ATP values have also been found in the frontal lobe of subjects with unipolar depression [94]. It is interesting that creatine levels were significantly lower in the right frontal lobe of the female subjects with bipolar disorder than male subjects [97]. These results suggest that bipolar depression and unipolar depression are associated with abnormal metabolisms of high energy phosphate. Abnormal energy metabolism in brain may be closely related to mood state of mood disorders and is also gender dependent. Frye et al. [98] used proton magnetic resonance spectroscopy to scan the anterior cingulate/medial prefrontal cortex and found that levels of glutamate + glutamine, glutamate and creatine + phosphocreatine were significantly higher in subjects with bipolar depression than healthy controls. Dager et al. [99], using two-dimensional proton echo-planar spectroscopic imaging, analyzed 32 medication-free outpatients with bipolar disorder predominantly in a depressed or mixed-mood state, and found that subjects with bipolar disorder have shown increased lactate levels and increased levels of total glutamate, glutamine and gamma-aminobutyric acid in gray matter (Tab. 1). Abnormal metabolism of high-energy phosphates and increased gray matter lactate suggest that bipolar disorder may be associated with mitochondrial dysfunction that induces an energy production shift from more efficient oxidative phosphorylation in mitochondrial electron transport chain to less efficient anaerobic glycolysis.

Mitochondrial energy production is produced via the process of oxidative phosphorylation coupled to the electron transport chain complex I–V (complex I, NADH coenxyme Q reductase; complex II, succinate dehydrogenase; complex III, coenzyme Q cytochrome c reductase; complex IV, cytochrome *c* oxidase; and complex V, ATP synthase). Studies indicate increased deletion and mutation in genes coding for complex I subunits in subjects with bipolar [100–102]. Recent DNA microarray analysis in *post mortem* frontal cortex and hippocampus revealed that expression of many mRNAs, coding for subunits of complex I–V, is decreased in subjects with bipolar disorder [103, 104]. Recent genotyping studies also suggest that polymorphisms of complex I subunit NDUFV2 are associated with bipolar disorder [105, 106]. Complex I is one of the main sites where electrons are leaked to oxygen, resulting in ROS production [107]. Abnormal function of ETC complex I in BD suggests ROS overproduction that may induce oxidative stress in this disease. We recently found that oxidative damage to lipids is increased in *post mortem* cingulate cortex of

Table 1 Brain chemical concentrations by tissue type* [99]

	Cho	Cre	NAA	mI	Glx	Lactate
Gray matter chemical concentration, mM						
Bipolar	2.52 (0.66)	9.41 (0.74)	10.60 (1.26)	4.59 (0.98)	17.80 (2.51)†	0.97 (0.24)†
Control	2.30 (0.26)	9.11 (0.73)	10.18 (0.43)	4.36 (0.50)	16.18 (1.85)	0.81 (0.16)
White matter chemical concentration, mM						
Bipolar	2.59 (0.35)	7.98 (0.84)	9.76 (0.89)	4.50 (0.62)	15.69 (2.60)	0.97 (0.25)
Control	2.49 (0.28)	7.58 (0.63)	9.77 (0.44)	4.25 (0.75)	14.51 (1.99)	0.91 (0.23)
White-gray matter chemical regression slope						
Bipolar	–0.10 (1.67)	2.26 (1.07)	1.31 (2.53)	–0.08 (1.45)	2.89 (2.79)	–0.21 (0.60)
Control	–0.39 (0.52)	2.13 (1.13)	0.35 (0.87)	–0.14 (1.03)	2.24 (2.46)	–0.35 (0.52)

Abbreviations: Cho, choline-containing compounds; Cre, creatine and phosphocreatine; Glx, glutamate, glutamine, and γ-aminobutyric acid; mI, *myo*-inositol; NAA, *N*-acetyl aspartate
* Values are given as mean (SD)
† $P < .01$ vs control

BD subjects [108]. Increased oxidative damage to lipids has also been found in blood samples of BD patients [109, 110]. Additionally, Benes et al. [111] reported that expression of antioxidant enzyme GST A4 and M3 subtypes are reduced in *post mortem* hippocampus from BD subjects. These findings suggest that impairment of energy production and mitochondrial dysfunction in bipolar disorder may induce oxidative stress.

Summary

Converging lines of study suggest cell loss and damage in key brain regions which may lead to decreased volume of prefrontal and limbic brain regions of subjects with bipolar disorder. Persistent changes in these brain regions may cause disturbance in the function of neuronal circuitry involved in mood regulation, subsequently resulting in impairment of neuroplasticity. These changes may have consequences for monoaminergic neurotransmitters including serotonin, a key intermediary in major depression and a target of antidepressant drugs. Many studies of bipolar depression have shown a decrease in the main metabolite of serotonin 5-HIAA in cerebrospinal fluid and a decrease in serotonin transporter binding activity in brain and platelets.

Mitochondria are enriched in the neuronal terminals and dendrites that form synaptic connections, and its major role is generation of ATP. Mitochondria are important in regulating synthesis, release, uptake and other functions of neurotransmitters, including serotonin, via energy production. Recent evidence has shown decrease of glucose, cerebral blood flow and energy metabolism in bipolar depression, indicating deficiency of energy production in this disease.

Studies also suggest defects of mitochondrial electron transport chain complexes and oxidative damage in bipolar disorder. Mitochondrial electron transport chain is not only a highly efficient way to store energy, but it is also the major resource for generating reactive oxygen species. Therefore mitochondrial dysfunction in bipolar disorder not only reduces energy production, but also causes overproduction of the reactive oxygen species that induce oxidative damage, resulting in impairment of neuroplasticity in specific brain regions related to mood regulation.

The neurobiology of bipolar disorder continues to be unraveled which will help us further understand the multidimensional nature of the illness and the predisposition to both manic and depressive symptoms. It is hard to draw conclusions about the neurobiology of bipolar depression, but in this chapter we have outlined several potential processes which may be relevant to understanding the basis of this phase and illness. Given the limited success of treatment for all phases of bipolar disorder, it seems very likely that further elucidation of the neurobiological mechanisms underlying bipolar depression holds great promise for the development of safe and more effective treatment for this disease.

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