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Bipolar Disorder: Diagnosis, Neuroanatomical and Biochemical Background

Kristina R. Semeniken[1,2] and Bertalan Dudás[2]
[1]*Department of Psychiatry, Millcreek Community Hospital, Erie, PA*
[2]*Neuroendocrine Organization Laboratory (NEO),*
Lake Erie College of Osteopathic Medicine (LECOM), Erie, PA
USA

1. Introduction

Bipolar disorder is a mood disorder that is characterized by episodes of mania or hypomania that often alternate with episodes of depression. Bipolar disorder is also referred to as manic-depressive disorder and bipolar affective disorder. This potentially disabling mood disorder has a lifetime prevalence of 4% in the US population (Ketter, 2010). According to the National Institute of Mental Health (NIMH), bipolar disorder is classified as severe in 82.9% of adult patients, with 25 being the average age of onset. As is the case with the majority of psychiatric disorders, bipolar disorder tends to run in families (Smoller and Finn, 2003).

Bipolar disorder varies in its presentation and may be difficult to diagnose. Diagnosis requires the presence of a manic or a hypomanic episode; however, it is likely that the first few episodes may present as bouts of depression, particularly in younger patients (Saddock and Saddock, 2003). According to the Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM-IV-TR; American Psychiatric Association, 2000) a distinct period of abnormal mood for at least one week is required to meet diagnostic criteria.

There are two major subtypes of bipolar disorder: type I and type II. Type I requires the presence of at least one manic or mixed episode. Mania is categorized by euphoria, impulsivity, distractibility, racing thoughts, irritability, decreased need for sleep and grandiosity. Individuals with mania may stay up all night cleaning or working on flamboyant projects, or they may engage in large spending sprees, gambling or substance abuse. Manic individuals often exhibit pressured speech which may be loud, verbose, and intrusive in nature. The thought process in mania is often disorganized with flight of ideas and loosening of associations. Manic individuals often have poor judgment and insight and they are likely to give unreliable case histories (Saddock and Saddock, 2003).

Manic episodes may vary in severity, with the more severe cases involving psychosis. About 75% of manic individuals experience some form of perceptual disturbance (Saddock and Saddock, 2003). Psychotic features of manic individuals are characterized by the presence of hallucinations and or delusions. These features may be congruent with the mood and may

revolve around possession of knowledge or power, disturbance in identity or belief in having relationship to a deity or famous person. Mood-incongruent psychotic symptoms do not focus on the themes mentioned above and are more likely to include thought insertion and delusions of being persecuted or controlled (Saddock and Saddock, 2003). Individuals suffering from bipolar disorder I may also experience mixed episodes. Mixed episodes often combine characteristics of a depressive episode with irritability, anxiety or inner tension, psychomotor agitation and racing thoughts (Koukopoulos and Koukopoulos, 1999; Ketter, 2010). Individuals experiencing mixed episodes are at highest risk for suicide, secondary to increased irritability and impulsivity combined with depressed mood (Goldberg et al., 1998; Akiskal and Benazzi, 2005).

Unlike bipolar I, bipolar disorder type II does not include full-blown manic episodes and it is often defined by episodes of hypomania combined with features of major depression and is considered to be less severe than bipolar I (Goodwin and Jamison, 1990). According to the DSM-IV-TR, hypomania is characterized by persistently elevated, irritable, or expansive mood lasting at least 4 days (as opposed to at least one week for mania). This mood must be distinct from the usual (nondepressed) mood. Although the mood disturbance in a hypomanic individual is observable by others, hypomanic episodes are not severe enough to cause marked impairment in social or occupational functioning, or to necessitate hospitalization (American Psychiatric Association, 2000). Additionally, psychotic features are absent from hypomania. Both mania and hypomania may be caused by comorbid states, such as hyperthyroidism or other medical conditions, hypothyroidism, electroconvulsive therapy (ECT) and medications such as antidepressants. In these cases, a diagnosis of bipolar disorder may not be established since diagnosis requires that the symptoms must not be due to a general medical condition or direct physiologic effects of a substance.

In bipolar disorder, episodes of mania or hypomania may alternate with episodes of depression. Episodes of depression are not exclusively limited to bipolar II and may also be present in bipolar I disorder. Depressive episodes involve either dysphoria (depressed mood) or anhedonia (loss of interest in pleasure). A major depressive episode is characterized by sadness or depressed mood, sleep disturbances (insomnia or hypersomnia), appetite disturbances, changes in body weight, suicidality, feelings of helplessness, hopelessness, worthlessness or guilt, loss of energy and loss of interest in activities (Saddock and Saddock, 2003). Individuals in a depressed episode may appear to be withdrawn and may exhibit slowing down of mental processes, known as psychomotor retardation. Not all depressed individuals admit to feeling depressed but they usually exhibit a negative outlook (Saddock and Saddock, 2003). During a depressive episode, patients may experience psychotic features such as hallucinations and or delusions. Patients in a depressed episode may also experience problems with memory and cognition. They may have problems concentrating or remembering recent events. Patients in a depressed episode are particularly at risk for suicide, with about 2/3 of them experiencing suicidal ideations (Saddock and Saddock, 2003). Comorbid states such as hypothyroidism and alcohol abuse may precipitate depression.

Bipolar disorder falls on a spectrum of severity. A less severe form is known as cyclothymia, which is characterized by cyclical mood swings that are less severe than full-blown mania or depression. Cyclothymia may involve hypomania but does not cause marked impairment in functioning and often involves a euphoric phase and a dysthymic

phase. The DSM-IV-TR criteria for rapid cycling include at least four episodes within a 12 month period. Patients with rapid cycling are more likely to be female and to have depressive and hypomanic episodes (Saddock and Saddock, 2003). At times, the presentation of bipolar disorder may not fit into any specific category and therefore will be classified as unspecified.

Bipolar disorder is a progressive illness, in which frequency of episodes increases over time with subsequent decreased probability of treatment response (Berk et al., 2010). Individuals suffering from bipolar disorder have been shown to have altered reward processing (Pizzagalli et al., 2008). Bipolar manic patients were observed to produce more errors in a two-choice selection task, suggesting impairment in making decisions during times of uncertainty about the success of the outcome (Minassian et al., 2004). Response-reversal studies involving medicated euthymic children with bipolar disorder showed that these children were slower to learn variable stimulus-reward contingencies (Gorrindo et al., 2005). Additionally, manic bipolar patients were observed to make more unfavorable choices when presented with two choices of variable favorability (Murphy et al., 2001). Both symptomatic and euthymic bipolar patients have been noted to demonstrate a decreased bias response toward more frequently rewarded stimuli, with anhedonic patients showing greater impairments in reward learning (Pizzagalli et al., 2008). The implication is that bipolar patients may have impairment in the long-term integration of reinforcements and may struggle with adapting their behavior to alterations in reward (Pizzagalli et al., 2008).

2. Neuroanatomy and bipolar disorder

Regulation of mood is believed to involve primarily two major neuroanatomic circuits: the limbic-thalamic-cortical circuit and the limbic-striatal-pallidal-cortical circuit (Mayberg, 1997; Soares and Mann, 1997). The limbic-thalamic-cortical circuit is also involved in working memory and includes the medial-dorsal nucleus of the thalamus, the ventrolateral prefrontal cortex and the amygdala (Floresco et al., 1999; Parsey et al., 2006). The limbic-striatal-pallidal-cortical circuit is involved in emotional expression (Drevets et al., 2008). Dysfunction in either of these circuits may result in a mood disorder (Parsey et al., 2006). Neuroanatomical changes of patients affected by bipolar disorder have been associated with a dysfunction in the prefrontal cortex, basal ganglia, temporal and frontal lobes of the forebrain as well as parts of the limbic system including amygdala, thalamus and striatum (Cerullo et al., 2009). Patients with bipolar disorder have also been found to have abnormalities in the subgenual anterior cingulate cortex (sACC) (Shah et al., 2009; Rosen and Rich, 2010). More specifically, decreased glial cell volume, regional cerebral blood flow, and decreased glial cell number have been observed in this region in bipolar patients, as opposed to healthy controls (Drevets et al., 1997; Ongur et al., 1998). Increased limbic activity has been found to be associated with aberrant emotional processing while neurophysiological abnormalities in the prefrontal cortex have been associated with impaired executive function (Green et al., 2007). Dysfunction in the prefrontal cortex, basal ganglia and the limbic system plays a significant role in bipolar disorder due to the strong connection between these regions and the emotional and cognitive aspects of affect regulation (Papez J.W., 1937; Allman et al., 2001; Vogt BA, 2005).

The nature and location of the neuroanatomical dysfunction in bipolar patients often correlates with the resulting symptoms. Abnormalities in the frontosubcortical circuit, especially in the hippocampus and the prefrontal cortex, may explain the attention impairment observed in manic patients (Sax et al., 1999). Reduced neuronal and glial density and glial hypertrophy have been identified in the hippocampus and the dorsolateral prefrontal cortex of patients with bipolar disorder (Rajkowska et al., 2001). These observations may account for cell loss observed in brain imaging and post-mortem studies of bipolar patients (Brown et al., 2003). These deficits differ from reported observations of increased neuronal density noted in patients with schizophrenia. The specific pattern of cell loss described above appears to resemble the reduced cell density found in patients with major depressive disorder (Rajkowska et al., 2001; Brown et al., 2003). Patients with bipolar disorder have less reduction of hippocampal volume than schizophrenic patients (Radonic et al., 2011). The hippocampus, particularly the CA3 region, plays an important role in the formation of declarative memory, which requires separate encoding of elements of an event and their organization in relation to one another (Preston et al., 2005). Impairment in the circuitry involved in formation of this type of memory may be responsible for the observed impairment in spatial memory and reward processing that has been noted in bipolar patients.

Individuals with bipolar disorder appear to exhibit altered responses to emotional stimuli, with apparent dysfunction in the ventral-limbic regions including the ventrolateral prefrontal cortex, the orbitofrontal cortex, the subgenual cingulate cortex, the insula, amygdala and striatum (Wessa and Linke, 2009). Dysfunction in the fronto-striatal-limbic network, which includes the structures mentioned above, has been associated with aberrant emotional processing, particularly with regard to misreading facial expression of emotions (Rosen and Rich, 2010). Increased striatal activity has been reported in bipolar patients in response to potentially rewarding stimuli (Hassel et al., 2008). Additionally, decreased activity has been noted in the dorsal brain structures including right dorsolateral prefrontal cortex, posterior cingulate cortex, and the dorsal anterior cingulate cortex of patients with bipolar disorder following exposure to significant emotional stimuli (Hassel et al., 2008; Wessa and Linke, 2009). It appears that imbalance between the ventral-limbic network and the dorsal brain structures may be responsible for the emotional dysregulation observed in bipolar disorder (Wessa and Linke, 2009).

Functional magnetic resonance imaging (fMRI) studies have shown a dysfunction of subcortical pre-frontal networks (striato-thalamic) and associated regions of the limbic lobe (Strakowski et al., 2005). Decreased modulation of medial temporal and subcortical structures in the anterior limbic lobe (striatum, amygdala and thalamus) by prefrontal areas has been noted to appear early in the course of the illness (Strakowski et al., 2005). The amygdala, which plays a role in the regulation of mood, is noted to be decreased in volume in bipolar patients. This decrease appears to be more severe as the patients get older (Doty et al., 2008), suggesting a correlation between progression of bipolar disorder and increasing abnormalities in the brain. Individuals in the early stages of bipolar disorder were found to have changes in the volume of the white matter, ventricles, amygdala, caudate nucleus, subgenual prefrontal cortex and putamen (Hajek et al., 2005). Moreover, the use of lithium for mood stabilization in bipolar disorder has been shown to increase the size of the amygdala and hippocampus (Yucel et al., 2007; Foland et al., 2008; Yucel et al., 2008). Other abnormalities found in the brains of bipolar patients using neuroimaging techniques have been noted to appear with recurrent episodes of mood instability and affect dysregulation.

These abnormalities have been observed in the lateral ventricles, cerebellar vermis and other prefrontal regions such as the left anterior prefrontal cortex (Strakowski et al., 2005). It appears that although abnormalities may be present at the onset, the severity of these lesions progresses with the disease.

3. The role of oxidative stress

Oxidative stress has been shown to play a role in the pathophysiology of bipolar disorder (Gawryluk et al., 2011). Alterations in oxidative enzymes as well as increased lipid peroxidation products and reactive oxygen species have been detected in individuals with bipolar disorder and other psychiatric diseases (Steckert et al., 2010). Reduced levels of glutathione in the brain have been reported in bipolar disorder as well as schizophrenia (Fullerton et al., 2010; Dean et al., 2011; Magalhaes et al., 2011). Along with glutathione reductions, evidence of oxidative damage to mitochondrial proteins have been noted in the brains of patients (Andreazza et al., 2010; Gawryluk et al., 2011). As the primary antioxidant in the body, glutathione acts as a free radical scavenger and has been noted to be present in high levels in the brain (Choy et al., 2010; Gawryluk et al., 2011). Decreased glutathione levels increase susceptibility of cells to oxidative stress (Gawryluk et al., 2011). Glutathione depletion has been associated with cognitive deficits such as disruption in short-term recognition memory and depression in psychiatric illnesses including bipolar disorder and schizophrenia (Choy et al., 2010). Glutathione replacement appears to improve these deficits. Administration of N-acetyl-cysteine (NAC), which is a precursor of glutathione, has been associated with improved short-term spatial memory in rats and with depression in humans (Choy et al., 2010; Magalhaes et al., 2011). Moreover, antioxidant effects of mood stabilizers including lithium and valproic acid have been observed in animal models of oxidant-induced mania (Jornada et al., 2011). These findings further support the role of oxidative stress in bipolar disorders while emphasizing the protective effects of mood stabilizers with regard to their proposed antioxidant effects on the brain.

4. Cortisol and HPA axis

There is a general consensus that the hypothalamic-pituitary-adrenal (HPA) axis plays a significant role in the pathophysiology of bipolar disorders. HPA regulates stress responses via stress hormones, including cortisol, adrenocorticotropic hormone (ACTH), corticotropin-releasing hormone (CRH) and arginine vasopression (AVP). CRH is released by hypothalamic neurons into the portal circulation and stimulates the release of ACTH from the anterior pituitary. Studies have found an enhanced response to CRH in bipolar manic individuals as compared to controls (Vieta et al., 1999). CRH stimulation has been shown to result in dysregulation of ACTH and cortisol response in bipolar disorder, leading to HPA axis dysregulation and altered cortisol release (Daban et al., 2005). The severity of both manic and depressive symptoms appears to correlate with the severity of HPA dysfunction (Daban et al., 2005). Interestingly, the changes in CRH secretion appear before symptoms become evident in bipolar individuals (Daban et al., 2005).

Increased HPA axis activity has been associated with depression, mixed manic states and less commonly with true manic episodes (Garlow S, 1999; Varghese and Brown, 2001; Manji et al., 2003). Elevated daytime cortisol levels were observed in the offspring of parents with

mood disorders, suggesting that cortisol excess may serve as a biomarker for susceptibility to developing bipolar disorder (Ellenbogen et al., 2011).

Since some of the morphological changes associated with chronic stress respond to mood stabilizers, chronic stress is believed to affect the development and progression of bipolar disorder (Wood et al., 2004). The complete evaluation of the extensive amount of data regarding the effects of chronic stress on brain morphology would certainly exceed the scope of the present chapter. Studies examining the human brain via MRI have noted decreased hippocampal volume in patients with post traumatic stress disorder (PTSD) and Cushing's syndrome, which are both conditions associated with excess cortisol levels (Manji et al., 2003). Of particular importance is the atrophy of CA3 hippocampal neurons which have been exposed to high levels of glucocorticoids (Sapolsky, 2000). Studies revealed that remodeling of apical dendrites on hippocampal CA3 pyramidal cells is mediated by adrenal steroids and excitatory amino acids (Wood et al., 2004). The threshold for cellular atrophy and death may be lowered by various pathological and physiological events including excitotoxicity from abnormal glutamatergic signaling enhancement and inhibition of glucose transport (Sapolsky, 2000). More importantly, these changes have been observed to be reversible and may even be prevented to some degree by pharmacological treatment with mood stabilizers (Wood et al., 2004).

5. Neurotransmitters involved in bipolar disorder

5.1 Norepinephrine

The dysfunctional behavior and mood dysregulation observed in mood disorders often involves abnormal neurotransmitter function. Monoamines are a class of neurotransmitters including dopamine, norepinephrine, epinephrine and serotonin. Neurochemical abnormalities involving monoamines have been observed in patients with bipolar disorder (Goodwin and Jamison, 1990; Fibiger, 1991; Willner et al., 1991; Schatzberg and Schildkrout, 1995; Manji H. and Potter W., 1997). Increased concentrations of norepinephrine have been found in the plasma and cerebrospinal fluid (CSF) of patients with bipolar mania (Goodwin and Jamison, 1990; Manji H. and Potter W., 1997). Increased norepinephrine turnover has also been noted in the thalamic and cortical areas in *post mortem* studies of individuals with bipolar disorder (Young et al., 1994; Vawter et al., 2000). On the other hand, norepinephrine was observed to be reduced to normal resting output in bipolar depressed patients (Manji and Lenox, 2000). *In vivo* studies have additionally revealed lower plasma levels of norepinephrine and its major metabolite, 3-methoxy-4-hydroxyphenylglycol (MHPG) in patients with bipolar depression as opposed to those with unipolar depression (Manji H. and Potter W., 1997). Urinary excretion of MHPG has also been noted to be higher in the manic state in comparison to the depressed state (Manji et al., 2003). The rate of norepinephrine turnover appears to be inversely proportional to the degree of depression, with higher turnover observed in more manic states. An explanation for this phenomenon may involve alteration in sensitivity of α_2 and β_2 adrenergic receptors in people with mood disorders (Schatzberg and Schildkrout, 1995). These observations suggest that bipolar individuals may be hypersensitive to fluctuations of norepinephrine levels, similarly to the noted hypersensitivity to acetylcholine in bipolar patients. Alterations in α_2 autoreceptor sensitivity may lead to increased activity of the α_2 autoreceptor, resulting in decreased release of norepinehprine, which subsequently affects mood (Manji and Lenox, 2000; Delgado and Moreno, 2000).

5.2 Dopamine

Dopamine is a catecholamine that has been shown to play a significant role in bipolar disorders (Cousins et al., 2009). Excess dopamine activity facilitates mania and delusional symptoms (Manji H. and Potter W., 1997; Serretti et al., 2001; Wightman and Robinson, 2002). Dopamine has also been proposed to play a role in the etiology of bipolar disorder. Manic states in healthy individuals that have received substances that increase dopaminergic activity (L-DOPA [the dopamine precursor L-3,4-dihydroxyphenylalanine], bromocryptine and amphetamine) have been observed (Murphy et al., 1971; Szczepankiewicz et al., 2011). Additional observations include the presence of manic symptoms following administration of high dose dopamine precursors to individuals with Parkinson's disease, with subsequent depressive state upon withdrawal of the dopamine precursor (Berk et al., 2007). Deficiency of dopamine has been suspected to play a role in the pathophysiology of depression. Reduced levels of homovanillic acid (HVA), a catecholamine metabolite that has been associated with dopamine, have consistently been found in the CSF of depressed and suicidal patients (Roy et al., 1992; Young et al., 1994; Manji H. and Potter W., 1997). These findings suggest that decreased neurotransmission of dopamine may correlate with depression and suicidality supporting the theory of catecholamine withdrawal in depressive states of bipolar disorder. It appears that dopamine excess correlates with manic states while dopamine depletion or withdrawal may precipitate depression. It has been suggested that the cyclical nature of bipolar disorder may result from potential downregulation of dopamine receptor sensitivity following excessive dopamine secretion (Berk et al., 2007).

Dopamine neurotransmission is primarily regulated by reuptake of dopamine from the synapse by the dopamine transporter (DAT) (Anand et al., 2011c). Dopamine binds to G protein-coupled receptors (D1, D2, D3, D4, D5), which then mediate its function in the nervous system (Beaulieu and Gainetdinov, 2011). The mechanism involving the DAT has been used as a marker for presynaptic dopamine function and has been found to be dysfunctional in individuals with bipolar disorder (Anand et al., 2011b). Significantly lower DAT availability has been found in the striatum of bipolar patients as opposed to healthy controls (Anand et al., 2011a). Animal studies revealed manic behavior traits such as increased risk-taking behavior in mice with reduced DAT function (Young et al., 2011), suggesting that reduced availability of the DAT results in subsequent increase in synaptic dopamine which therefore facilitates mania (Fig.1).

The pivotal role of dopamine in the pathomechanism of the bipolar disorders is supported by the observation that excessive dopamine levels observed in mania can be effectively treated with antipsychotic medications, whose mechanism involves dopamine blockade (Greenwood et al., 2001). Conversely bupropion (Wellbutrin), which binds to the dopamine transporter and also inhibits reuptake of norepinephrine, has been shown to be effective in treating bipolar depression (Sachs et al., 1994).

5.3 Serotonin

Abnormalities in the indolamine serotonin (5-HT) have also been observed in bipolar disorder. Studies examining hippocampal 5-HT_{1A}, 5-$HT_{2A,}$ and 5-HT_{1B} mRNA and 5-HT_{1A} and 5-HT_{2A} receptor mRNA in the dorsolateral prefrontal cortex have revealed increased serotonin mRNA levels and decreased 5-HT_{2A} mRNA levels in the hippocampal formation

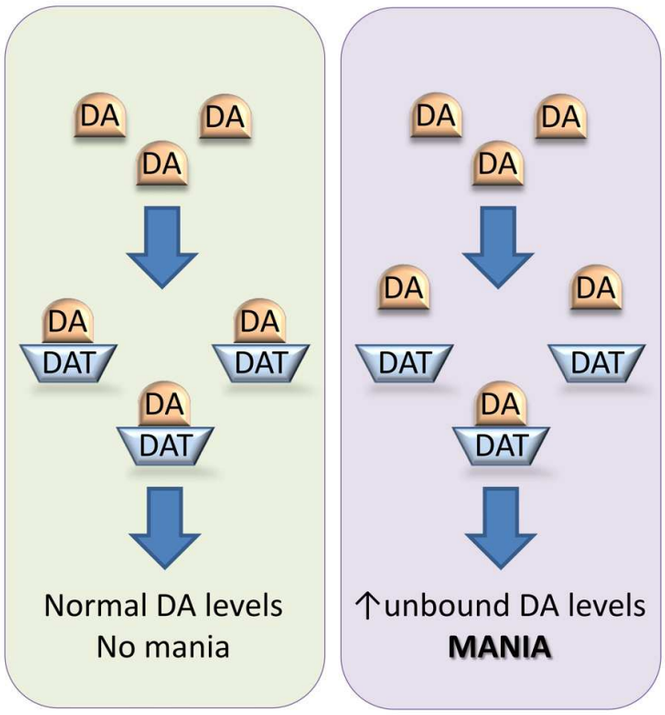

Fig. 1. The role of dopamine transporter (DAT) in the pathogenesis of mania.

of bipolar and schizophrenic patients (Lopez-Figueroa et al., 2004). Studies have found a correlation between major depressive episodes and altered serotonergic neurotransmission (Maes et al., 1995; Garlow S, 1999). Decreased radioligand binding to the serotonin transporter has been noted in the midbrain and platelets of individuals with depression (Garlow S, 1999). Reduction in central serotonergic activity has been found in bipolar individuals who were in the depressed phase, with similar findings in euthymic bipolar patients (Mahmood and Silverstone, 2001; Chou et al., 2010). Further studies reported decreased 5-HT_{1A} receptor binding in the hippocampus, amygdala and raphe in bipolar depressed patients, depressed relatives of bipolar patients as well as other individuals suffering from depression (Drevets et al., 1999). However, increased levels of 5-HT_{1A} were noted in depressed males with bipolar disorder (Sullivan et al., 2009). These findings indicate an increase in autoreceptor binding which may lead to decreased release of serotonin with a subsequent upregulation of postsynaptic 5-HT_{1A} receptors (Sullivan et al., 2009). Increased cortisol secretion has been proposed as one explanation for the decrease in 5-HT_{1A} receptor binding in depressive states, particularly since stimulation of corticosteroid receptors has been associated with inhibition of postsynaptic 5-HT_{1A} receptor mRNA expression in some regions of the brain (Manji et al., 2003). These data support the observation that the onset of bipolar symptoms and recurrence of manic and depressive episodes are more likely to occur during times of stress.

Models involving tryptophan depletion have further explored the role of serotonin in bipolar disorder. Tryptophan depletion lowers the levels of serotonin (Manji et al., 2003) and associated with recurrence of depression secondary to a reversed response to antidepressant medications in patients with a mood disorder but no onset or worsening of depression in

nonmedicated depressed patients, healthy individuals without mental illness or in lithium-treated euthymic patients with bipolar disorder (Delgado et al., 1999; Hughes et al., 2000). Research has examined unaffected relatives of patients with bipolar disorder in order to investigate if sensitivity to cognitive effects of serotonin decrease might serve as a heritable marker or endophenotype for bipolar disorder (Manji et al., 2003). One double-blind crossover design study examined 20 unaffected relatives of bipolar patients and 19 control subjects undergoing acute tryptophan depletion (ATD). The study revealed that unaffected relatives of bipolar patients exhibited increased impulsivity and depressed mood following ATD as opposed to placebo (Sobczak et al., 2002). These symptoms were not observed in healthy controls. Additionally, unaffected relatives were found to have decreased number of lower affinity binding sites for imipramine and lower platelet concentrations of serotonin independent of ATD administration. Further studies revealed impairment in planning and memory in first degree healthy relatives of bipolar type I patients independent of ATD as well as impaired speed of information processing in first degree healthy relatives but not in healthy controls following ATD (Sobczak et al., 2002). These data suggest that impairments in serotonin metabolism observed in bipolar patients may be inherited.

A reduction in the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) was observed in patients with bipolar disorder as well as other mood disorders (Young et al 1994). This reduction was especially noted in individuals with aggression, impulsivity and suicide attempts (Manji et al., 2003). However, data regarding the 5-HIAA levels in manic versus depressed individuals is rather controversial. Some studies did not find a difference in CSF 5-HIAA levels between manic and depressed patients (Goodwin and Jamison, 1990), while others noted decreased 5-HIAA in the CSF in both manic and depressed individuals compared to controls as well as a significant decrease in CSF 5-HIAA accumulation in manic individuals as compared to their depressed counterparts and to controls (Goodwin and Jamison, 1990). Despite the inconsistent results, decreased CSF levels of the serotonin metabolite 5-HIAA appear to correlate with impulsive, aggressive behavior and mania, emphasizing the role of serotonin in the pathophysiology of bipolar disorder.

5.4 Glutamate

Abnormalities in glutamate and glutamate receptor functioning have been noted in patients with bipolar disorder. Glutamate is a major excitatory neurotransmitter affecting cognition, learning and memory (Shigeri et al., 2004). While glutamate mediates information affecting cellular survival, formation and destruction of synapses and brain development, it may be neurotoxic if not present in the right concentrations at appropriate locations and time in the nervous system (Danbolt, 2001). Stress-induced hippocampal changes in the brains of patients with bipolar disorder have been noted to include alterations in glutamate and its receptors. Patients with bipolar disorder have been found to have elevated lactate and glutamate levels (Dager et al., 2004). Elevated glutamate levels have been noted particularly in the dorsolateral prefrontal cortex of patients with acute mania (Michael et al., 2003). Elevated glutamate neurotransmission has been reported in bipolar patients and has been suggested as the reason for elevated glutamate levels in the cortex (Eastwood and Harrison, 2010). More specifically, increased expression of the vesicular glutamate transporter (VGluT1), which is expressed in glutaminergic neurons, has been found in the anterior cingulate cortex of bipolar patients (Eastwood and Harrison, 2010). VGluT1, netrin-G1 and

its isoforms Gqc, G1d and G1f, as well as netrin-G2 are axon guidance and cellular adhesion molecules (Eastwood and Harrison, 2010). They participate in formation and maintenance of glutamatergic synaptic connections (Eastwood and Harrison, 2010). Netrin–G expression was also found to be elevated in the right anterior cingulate cortex of bipolar patients (Eastwood and Harrison, 2010). Netrin-G molecules have been known to affect the formation and plasticity of excitatory pathways (Eastwood and Harrison, 2010), suggesting that their increased expression may lead to increase in glutamate neurotransmission and possible neurotoxicity in the brains of bipolar patients.

5.5 GABA

Abnormal levels of gamma amino butyric acid (GABA) have been identified in bipolar disorder. GABA is an inhibitory neurotransmitter which modulates the activity of other neurotransmitters in the central nervous system (Vuoristo J, 2011). It is synthesized from glutamate, with the enzyme glutamate decarboxylase playing a key role in its synthesis (Bielau et al., 2007) (Fig.2). GABA plays a role in modulating hippocampal and cortical circuits and is involved in discriminative information processing, integrating sensory information and generating oscillatory rhythms in the corticolimbic system (Sakai et al., 2008). GABA participates in the inhibition of aggressive and impulsive behaviors, which are often prevalent in bipolar disorder, particularly in mixed and manic states (Sakai et al., 2008). GABA deficits as well as decreased inhibitory activity have been reported in the cortex of individuals with bipolar disorder (Duffy et al., 2000; Levinson et al., 2007). Aberrant modulation of GABA interneurons by glutamate has been noted to occur via the NR2A subunit of the N-methyl-D-aspartate (NMDA) receptor in the cerebral cortex (Woo et al., 2004). Decreased NR2A mRNA has been observed in bipolar patients, particularly in layer 2 of the anterior cingulate cortex (Woo et al., 2004). Decreased plasma levels of GABA have also been implicated in bipolar mania as well as in bipolar depression (Petty, 1995). Animal studies have revealed decreased GABA function in states of depression with subsequent improvement in mood following administration of GABA agonists (Petty, 1995). Interestingly, it has been reported that GABA levels do not normalize following treatment or remission of depression (Duffy et al., 2000). *Post mortem* studies examining GABA in humans noted significantly decreased protein in $GABA_b$ receptor subunits (BABBR1 and GABBR2) in the cerebellum of individuals with schizophrenia, bipolar disorder, autism and depression as compared to healthy controls (Fatemi et al., 2011). It appears that these deficits may be treatable as various classes of antidepressants have been reported to cause an up-regulation of $GABA_b$ receptors (Duffy et al., 2000). Additionally, mood stabilizing medications such as valproate, carbamazepine, gabapentin, and lithium carbonate have been noted to alter GABA levels, possibly decreasing aggressive and impulsive behavior by increasing availability and efficacy of GABA (Sakai et al., 2008).

5.6 Substance P

Substance P is a neuropeptide that is widely distributed throughout the central and peripheral nervous system (Pioro et al., 1990; Dudas and Merchenthaler, 2002; Lieb et al., 2003) and it has been shown to play a role in the pathomechanism of bipolar disorder (Lieb et al., 2003). Substance P regulates the release of acetylcholine in the cortex and co-localizes with dopamine in the midbrain and striatum, with GABA in the cortex, and with serotonin

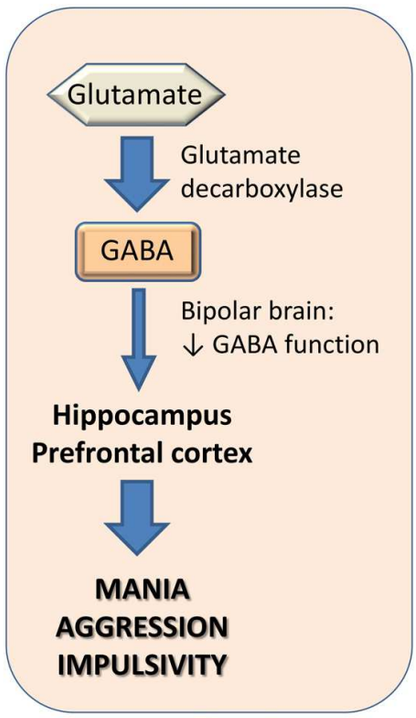

Fig. 2. Role of GABA in the pathogenesis of mania.

in the raphe nuclei (Jakab et al., 1997). Substance P, along with its receptor, the neurokinin 1 receptor (NK1R), is distributed in numerous areas of the brain including hippocampus, amygdala, frontal cortex and hypothalamus, and it appears to be involved in regulating responses to stress and fear (Herpfer and Lieb, 2005). Alterations of substance P content in these regions have been noted to influence the stress response and affective states (Lieb et al., 2003). Administration of substance P produces fear-related behaviors while blockade of NK1/2R or NK1/2/3R is associated with anxiolytic effects (Herpfer and Lieb, 2005). Moreover, an antidepressant effect has been noted when using substance P receptor antagonists, such as L-759274 and MK-869 (Mendlewicz et al., 2005). Substance P facilitates synthesis of interleukin-6 (IL-6), a cytokine, whose levels have been reported to be elevated in acute depressive states of bipolar disorder (Lieb et al., 2003). Inhibition of substance P as well as NK1R down-regulation has been noted following valproic acid administration (Lieb et al., 2003).

5.7 Acetylcholine

Acetycholine, along with cortisol, monoamines and amino acids has been suggested to play a role in the pathophysiology of bipolar disorder (Chen et al., 2010). Several studies reported catecholaminergic and cholinergic imbalance in bipolar patients. Administration of cholinomimetic agents and cholinesterase inhibitors reduced manic symptoms in bipolar manic patients (Davis et al., 1978; Fritze and Beckmann, 1988). Indeed, administration of the cholinergic agent physostigmine has been shown to result in decrease of manic symptoms in manic individuals as well as increase in depressive symptoms in non-manic individuals (Janowsky et al., 1974; Fritze and Beckmann, 1988). Animal models have noted exaggerated

neuroendocrine and behavioral responses in response to administration of cholinergic agents (Overstreet et al., 1988; Janowsky et al., 1994). Moreover, rats bred for cholinergic sensitivity were noted to be more aggressive (Pucilowski et al., 1990). It appears that individuals with bipolar disorder may be more sensitive to the effects of acetylcholine. Studies involving humans have noted increased sensitivity to the effects of physostigmine administration in patients with affective disorders (Oppenheim et al., 1979; Risch et al., 1981). More specifically, euthymic patients with bipolar disorder were noted to become depressed after physostigmine administrations as compared to healthy controls (Oppenheim et al., 1979). Interestingly, previous data also reported increased serum epinephrine levels following administration of a cholinergic agent, suggesting that increased cholinergic tone may precipitate a subsequent increase in adrenergic tone (Janowsky et al., 1986).

6. The role of genes

According to the kindling theory, the likelihood of developing bipolar disorder increases in response to a series of stressful events in predisposed individuals (Saddock and Saddock, 2003). Studies involving adoption, twins and family reveal a genetic predisposition to developing bipolar disorder (Gershon et al., 1990; Muglia et al., 2002). A multitude of genes interacting with each other as well as with the environment is most likely lead to a multifactorial mode of inheritance for bipolar disorder (Berrettini W.H, 1999; Muglia et al., 2002). A significant association was reported between two single nucleotide polymorphisms (rs4952 and rs4953) in the human beta 3 nicotinic acetylcholoine receptor subunit gene (CHRNB3) on chromosome 8 and bipolar disorder (Hartz et al., 2011). Additionally, genetic linkage studies suggest a role for human alpha7 nicotinic acetylcholine receptor subunit gene (CHRNA7) on chromosome 15q13-q14 as one of the candidate genes for bipolar disorder (Hong et al., 2004). Interestingly, linkage to CHRNA7 has also been reported in schizophrenia and schizoaffective disorder, suggesting a similar genetic cause for these two disorders (Leonard et al., 2001; Martin et al., 2007). Other studies examining chromosome 15 have found a genetic association between bipolar disorder and GABA-A receptor ra5 subunit gene locus (GABRA5) on chromosome 15q11-q13 (Otani et al., 2005). Low GABA function has been proposed to be a heritable marker for susceptibility to developing a mood disorder and GABRA5 may be associated with bipolar disorder (Petty, 1995; Papadimitriou et al., 2001).

Variants in the interleukin-1 (IL-1) cluster on chromosome 2q13 has also been associated with increased risk for both schizophrenia and bipolar disorder (Papiol et al., 2008). Specific genetic polymorphisms of the IL-1B gene from the IL-1 gene cluster have been associated with grey matter deficits in the brain of bipolar disorder patients (Papiol et al., 2008). Altered or increased expression of proinflammatory genes has been reported in monocytes of individuals with bipolar disorder as well as their offspring (Padmos et al., 2008). This pattern of gene expression is a possible etiological cause for the increased oxidative state reported in bipolar disorder.

The short arm of chromosome 11 has been investigated for possible genetic factors leading to developing bipolar disorder. This particular region incorporates the tyrosine hydroxylase (TH) and the dopamine D4 receptor gene (DRD4) (Todd et al., 1996; Oruc et al., 1997; Furlong et al., 1999; Li et al., 1999; Serretti et al., 2001). Tyrosine hydroxylase plays a

significant role in the formation of dopamine since it is the key and rate-limiting enzyme of the catecholamine synthesis converting tyrosine to DOPA, a precursor of dopamine (Muglia et al., 2002). DRD4 has been noted to be highly polymorphic, consisting of 2-10 tandem repeats in the third exon, encoding the receptor's longest loop (Asghari et al., 1995; Muglia et al., 2002). The gene for tyrosine hydroxylase contains a microsatellite known as HUMTH01, which has been proposed to play a regulatory role in its expression (Meloni et al., 1998). Studies investigating the short arm of chromosome 11 have been inconsistent, with many of them reporting lack of evidence for association with DRD4 and development of bipolar disorder (Byerley et al., 1992; Sidenberg et al., 1994; Smyth et al., 1996; Malafosse et al., 1997). Likewise, a positive and negative association has been observed between HUMTH01 and bipolar disorder (Serretti et al., 2000; Muglia et al., 2002). Studies examining a sample of nuclear families of bipolar patients and their biological parents reported a parent of origin effect (POE) for the DRD4 alleles 2- and 4- repeat alleles, which was inherited from the mother. This effect was noted to be located on chromosome 11p15.5, which is close to a group of imprinted genes (Muglia et al., 2002), indicating that genomic imprinting may be associated with bipolar disorder.

The dopamine transporter (DAT) gene plays a vital role in transmission of dopamine by mediating dopamine uptake into the synaptic terminal (Greenwood et al., 2001). Increased dopamine concentrations have been observed after administration of cocaine and amphetamine, which have been proposed to act at the DAT to inhibit reuptake of dopamine (Giros et al., 1992). Studies examining DAT for linkage to bipolar disorder in families from the Old Order Amish, Icelandic pedigree and the general North American population revealed a locus on chromosome 5p15.3 near the DAT gene, suggestive of autosomal dominant inheritance of bipolar disorder (Kelsoe et al., 1996; Homer et al., 1997). More specifically, data suggest that a functional variant of a 3′ noncoding sequence element may influence susceptibility for bipolar disorder (Greenwood et al., 2001). The significance of DAT in bipolar disorder is based on its involvement in regulating synaptic reuptake of dopamine (Kelsoe et al., 1996). Chromosomal aberration near the DAT gene locus in bipolar patients correlates with abnormalities in dopamine neurotransmission observed in bipolar disorder indicating a genetic predisposition to developing the disorder.

Dysregulation of the serotonin transporter and abnormalities in serotonin metabolism have also been noted in studies of patients with affective disorders. Serotonin transporter is involved in serotonin regulation and is the site of action for numerous antidepressants (Kelsoe et al., 1996). It is noteworthy that the serotonin transporter polymorphism (5-HTTLPR) gene as well as brain-derived neurotrophic factor (BDNF) polymorphism have been linked with suicidality in bipolar patients (Vincze et al., 2008). The 5-HTTLPR variant is the promoter region of the serotonin transporter gene, which has two alleles: the long 'l' allele and the short 's' allele (Neves et al., 2008). The short 's' allele of the 5-HTTLPR has been associated with significantly lower activation of the ventral anterior cingulate cortex, a dysfunction observed in bipolar patients (Shah et al., 2009). In addition to its link to bipolar disorder, 's' allele is particularly associated with suicidal behavior (Neves et al., 2008; Ferreira et al., 2009). Interestingly, mania and suicidality have been repeatedly observed in bipolar individuals following treatment with antidepressants (Ferreira et al., 2009). Since depression is often treated by selective serotonin reuptake inhibitors (SSRIs), understanding this mechanism can encourage more careful assessment and diagnosis of bipolar patients.

7. Concluding remarks

Bipolar disorder is a progressive illness which, if left untreated, results in cognitive decline. The rate and nature of the progression of the disease varies among individuals. The pathology of the bipolar disorder includes a variety of abnormalities in the neuroanatomy, endocrine homeostasis, neurotransmitter functions and genes of the patients.

Reduced hippocampal volume, dysfunction in the prefrontal cortex and limbic system observed in patients suffering in bipolar disorder emphasizes the importance of these brain regions in the development of the disease. The nature and extent of these neuroanatomical changes vary with the presentation, severity, and duration of the disease. While some anatomical abnormalities may be present prior to onset of disease, these lesions may become more severe with the progression of the disease. Conversely, certain abnormalities may be amendable to treatment. Additional factors involved in the development and progression of bipolar disorder include abnormal HPA axis function and oxidative stress. Abnormalities in neurotransmitter function, including dopamine, norepinephrine, serotonin, GABA, acetylcholine, glutamate and substance P have also been observed in bipolar disorder, offering the possibility of various avenues of pharmacologic interventions. Genetic variations found in bipolar patients indicate a predisposition in the development of the disease. The diversity of the factors involved in the pathomechanism of bipolar disorder may explain the wide variety of clinical manifestations and consequently may offer a broad range of options for successful treatment of this debilitating disease.

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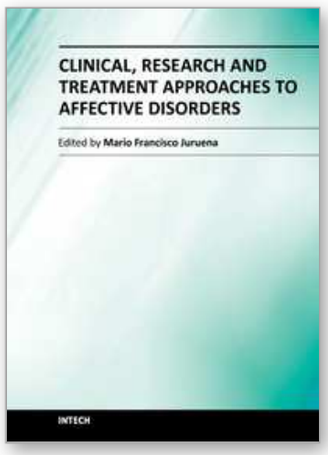

Clinical, Research and Treatment Approaches to Affective Disorders

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The causes, development and outcomes of disorders are determined by the relationship of psychological, social and cultural factors with biochemistry and physiology. Biochemistry and physiology are not disconnected and different from the rest of our experiences and life events. This system is based on current studies that report that the brain and its cognitive processes show a fantastic synchronization. Written by the foremost experts on Affective Disorders worldwide, this book is characterized by its innovative, refreshing, and highly sensitive perspective on current knowledge of diagnostic, neurobiology, early life stress and treatment of Mood Disorders. The authors share a deep understanding of unique challenges and difficulties involved in Affective Disorders, and have achieved a balance among clinical, research and new treatment approaches to Affective Disorders. The chapters are written in a comprehensive, easily readable, and highly accessible style, stimulating readers, clinicians and researchers.

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51000 Rijeka, Croatia
Phone: +385 (51) 770 447
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Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
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