

## Treatment of Bipolar Disorder according to a Neural Network

Felix-Martin Werner<sup>1,2\*</sup> and Rafael Coveñas<sup>2</sup>

<sup>1</sup>Higher Vocational School of Elderly Care and Occupational Therapy, Euro Academy Pößneck, Pößneck, Thuringia, 07381, Germany

<sup>2</sup>Laboratory of Neuroanatomy of the Peptidergic Systems (Lab. 14), Institute of Neurosciences of Castilla y León (INCYL), University of Salamanca, Salamanca, Castilla-León, 37007, Spain

### Abstract

Here, we describe the alterations of excitatory neurotransmitters (dopamine, serotonin, noradrenaline, acetylcholine), glutamate and GABA (a presynaptic inhibitory neurotransmitter) in the brain areas (brainstem, hypothalamus, hippocampus) involved in bipolar disorder. The coherence between the pituitary hypothalamic-adrenocortical axis and the existing neurotransmitter alterations is pointed out. Neural networks are described in the concerned brain areas, including the neurotransmitters and the depending subreceptors, on which the prophylactic drugs exert their effects. A survey of the commonly used prophylactic drugs is also given.

**Keywords:** Bipolar disorder; Mania; Depressive state; Dopamine; Noradrenaline; Serotonin; Acetylcholine; GABA; Glutamate; Second-generation antipsychotic drug; Mood-stabilizing drug

### Introduction

Bipolar disorder is an affective psychosis with alternating depressive, manic or mixed symptoms. In the depressive phase, in patients suffering from bipolar disorder, a hypoactivity of noradrenaline and serotonin occurs in the brainstem as well as in the hippocampus for dopamine [1]. Moreover, alterations in the brainstem and hippocampus of the presynaptic inhibitory neurotransmitter GABA and glutamate, which mainly is an excitotoxic neurotransmitter and partly a presynaptic inhibitory neurotransmitter, can be observed [2]. In manic symptoms, both D<sub>2</sub> dopamine hyperactivity and 5-HT<sub>2A</sub> serotonin dysfunction were found in the hippocampus. The presynaptic neurotransmitter GABA and glutamate are also involved in the pathophysiology of manic symptoms. The dysfunction of the hypothalamic-pituitary-adrenocortical (HPA) axis will be described [3]. Neural networks in the brainstem, hypothalamus and hippocampus will be also pointed out and the dysfunctions of the HPA axis will be deduced [3]. Bipolar disorder is mainly treated by mood-stabilizing drugs such as lithium, valproate and lamotrigine or second-generation antipsychotic drugs such as risperidone, olanzapine, quetiapine or aripiprazole.

### The Pituitary-Hypothalamic-Adrenocortical Axis in Affective Symptoms

Depressive and manic symptoms are associated with a dysfunction of the HPA axis [3]. In depressive symptoms, reduction of cortisol levels and an increase of corticotropin-releasing hormone (CRH) levels were found, and an enhanced response in the dexamethasone (DEX)/CRH test was also observed [4]. In first-episode depressive patients, the thickness of the lateral orbitofrontal cortex was significantly reduced and it was associated with increased cortisol levels, which occurred in 50% of the patients [5]. Leonard [6] reported the coherence between the HPA axis and the serotonergic system [6]. In the section about the neural networks, it will be pointed out that CRH-containing neurons located in the hypothalamus transmit via CRH<sub>1</sub> receptors a strong activating impulse to glutaminergic neurons, which strongly inhibit, via metabotropic 5 glutaminergic (m5Glu) receptors, 5-HT<sub>1A</sub> serotonergic neurons located in the brainstem [4]. CRH<sub>1</sub> containing neurons located in the hypothalamus also activate GABAergic neurons which presynaptically inhibit, via GABA<sub>A</sub> receptors, D<sub>2</sub> dopaminergic neurons located in the hippocampus [7]. Depressive or manic symptoms

only occur when the susceptibility genes are present. The serotonin transporter gene can induce serotonin hypoactivity in the brainstem, which is correlated with depressive symptoms [7]. The glutamic acid decarboxylase (GAD) 67, which encodes GABA hypofunction, and the monoamine oxidase A/B gene, which encodes dopamine hyperactivity through a decreased breakdown, can lead to manic symptoms.

### Alterations of Classical Neurotransmitters and Neuropeptides in the Brain Regions Involved in Bipolar Disorder

In bipolar disorder, a few brain regions (brainstem, hypothalamus, hippocampus) are involved in depressive and manic symptoms. Biela et al. [8] examined the volumes of the striato-pallidal nuclei, hypothalamus, thalamus, amygdala, hippocampus and basal limbic forebrain of patients with major depression and bipolar disorder and they found volume differences in all the investigated regions with strong volume differences contributed by the hypothalamus, external pallidum, putamen and thalamus [8]. These regions show alterations in classical neurotransmitters and neuropeptides [1,7]. Thus, the hypo- or hyper-activity of postsynaptic excitatory neurotransmitters (noradrenaline, serotonin, dopamine, acetylcholine) and the actions of glutamate and GABA (a presynaptic inhibitory neurotransmitter) acting at specific subreceptors, will be pointed out [1,7].

### Noradrenaline

In the depressive symptoms of the bipolar disorder, a hypoactivity of noradrenaline occurs in the brainstem. Hereby, a reduced activation of the noradrenergic alpha1 receptor, starting from the locus coeruleus, can be observed [9]. In depressive states, a serotonin and noradrenaline

**\*Corresponding author:** Felix-Martin Werner, Neural Networks in Neurological and Psychiatric Diseases, University of Salamanca, Instituto de Neurociencias de Castilla y León (INCYL), Laboratorio de Neuroanatomía de los Sistemas Peptidérgicos (Lab. 14), c/ Pintor Fernando Gallego, 1, 37007-Salamanca, Spain, Tel: +34/923/29 44 00, Extension 1856; Fax: +34/923/29 45 49; E-mail: felixm-werner@versanet.de

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reuptake inhibitor, for example venlafaxine, can be administered but the dosage must be chosen carefully, because an activation of the noradrenergic neurotransmission can induce noradrenaline hyperactivity and may promote hypomanic symptoms [10].

### Dopamine

In the hippocampus and the extrapyramidal system, dopamine, acting mainly at D<sub>2</sub> receptors, shows hypoactivity in depressive symptoms and hyperactivity in manic symptoms [4]. The noradrenaline and dopamine reuptake inhibitor, bupropion, which is used to treat the “decreased positive effect”, i.e. loss of energy, interest and pleasure in major depression, and that shows a good therapeutic effect [11], cannot be administered in depressive symptoms in bipolar disorder, because the activation of the dopaminergic neurotransmission can induce dopamine hyperactivity and hence hypomanic symptoms [10].

### Serotonin

Serotonin transporter genes linked polymorphic regions, also called 5HTTLPR, are supposed to encode symptoms in bipolar disorder type 1 [12]. In depressive symptoms, hypoactivity of serotonin, acting at 5-HT<sub>1A</sub> receptors, occurs in the brainstem. However, other subreceptors also play an important role in the pathogenesis of bipolar disorder. In the hippocampus, the dysfunction of 5-HT<sub>2A</sub> receptors is involved in depressive and manic symptoms [13]. The American society of clinical psychopharmacology asked participating psychopharmacologists about their treatments of major depression in bipolar disorder [14]. When the patients were treatment-resistant to selective serotonin reuptake inhibitors (SSRIs), the psychopharmacologists chose bupropion, a selective noradrenaline and dopamine reuptake inhibitor and, if this drug was contraindicated for causing hypomania, they mostly chose a second-generation antipsychotic drug, for example olanzapine, aripiprazole or quetiapine combined with the mood-stabilizing drug lamotrigine [14].

### Acetylcholine

In bipolar disorder, the catecholaminergic-cholinergic hypothesis has been reconsidered [15]. In depressive states, an increased activity of acetylcholine can be found and, in mania, an increased activity of catecholamines (dopamine and noradrenaline) occurs. The increased activity of acetylcholine, in depressive states, is mediated via muscarinic and nicotinic cholinergic receptors [15]. In a previous work on neural networks [7], a neurotransmitter balance has been described between serotonergic, noradrenergic and dopaminergic neurons. In the hippocampus, nicotinic cholinergic neurons activate D<sub>2</sub> dopaminergic neurons via alpha4beta2 nACh (nicotinic cholinergic) receptors, and hence the activation of these receptors can promote antidepressant effects [7].

### Gamma-aminobutyric acid (GABA)

In both schizophrenia and bipolar disorder, altered hippocampal neural networks have been described [16]. The hippocampus of patients suffering schizophrenia and bipolar disorder have been studied and specific proteins have been detected [16]; the data suggest that in these patients both an altered oxidative stress response and an altered mitochondrial function occurred [16]. In both diseases, these findings hint at an alteration of hippocampal GABAergic interneurons [16]. In depressive symptoms, GABAergic neurons via GABA<sub>B</sub> receptors strongly presynaptically inhibit brainstem alpha1 noradrenergic neurons [17]. In manic symptoms, GABAergic neurons via GABA<sub>A</sub> receptors could weakly inhibit D<sub>2</sub> dopaminergic neurons located in the hippocampus, inducing dopamine hyperactivity [18].

### Glutamate

In bipolar disorder, a glutamate dysfunction via N-methyl-D-aspartate (NMDA) and metabotropic glutaminergic receptors occurs in the brainstem and hippocampus [19]. Glutaminergic neurons weakly inhibit, via m5Glu receptors, 5-HT<sub>1A</sub> serotonergic neurons located in the “mood center” of the brainstem. Consequently, m5Glu receptor antagonists could exert antidepressant properties [20]. In the hippocampus, glutaminergic neurons weakly or strongly inhibit 5-HT<sub>2A</sub> serotonergic neurons and can induce depressive symptoms, with glutamate hyperactivity and serotonin hypoactivity, or manic symptoms with serotonin hyperactivity through a reduced presynaptic glutaminergic inhibition [18].

### Galanin

In depressive symptoms, galanin levels were found to be decreased in the hypothalamus. After treatment with a SSRI, galanin levels increased [21].

### Neuropeptide Y

In the cerebrospinal fluid (CSF), neuropeptide Y levels decreased in depressive states and increased after an antidepressant treatment [4]. Neuropeptide Y-containing neurons located in the dentate gyrus weakly inhibit, via NPY<sub>1</sub> receptors, hippocampal GABAergic neurons [22].

### Substance P

In the CSF, substance P levels increased in patients showing depressive symptoms but decreased after an antidepressant treatment. Antagonists of the subreceptor of the substance P, the NK<sub>1</sub> receptor, only have a weak antidepressant effect. Substance P-containing neurons weakly activate, via NK<sub>1</sub> receptors, hippocampal GABAergic neurons [22].

### Neural Networks in the Brain Regions Involved in Bipolar Disorder

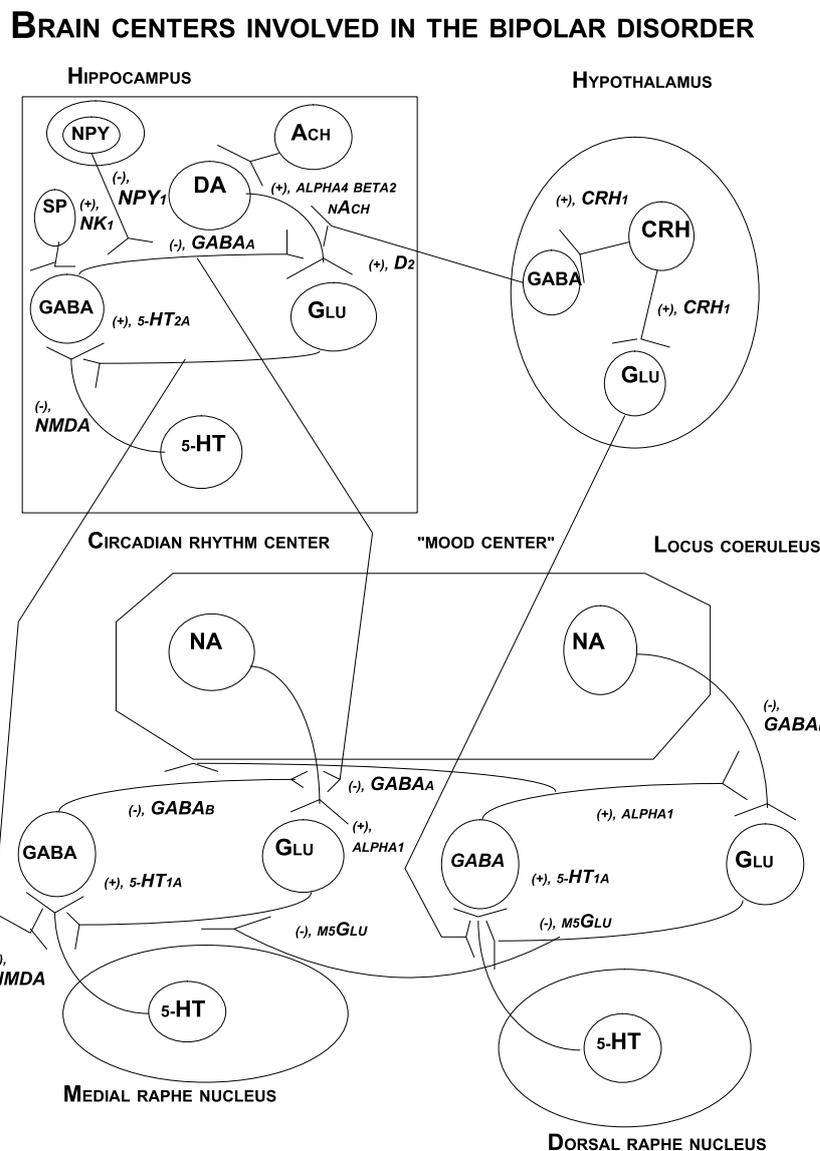
The neural networks in the brain areas involved in bipolar disorder, namely brainstem, hypothalamus and hippocampus, can be described as follows: in the “mood center” of the brainstem, serotonergic neurons from the dorsal raphe nucleus transmit a weak activating impulse via 5-HT<sub>1A</sub> receptors to GABAergic neurons, which inhibit via GABA<sub>B</sub> receptors noradrenergic neurons located in the locus coeruleus. The latter neurons activate, via alpha1 receptors, glutaminergic neurons which inhibit, via m5Glu receptors, 5-HT<sub>1A</sub> serotonergic neurons. GABAergic neurons inhibit, via GABA<sub>B</sub> receptors, other GABAergic neurons located in the center of the circadian rhythm which inhibit, via GABA<sub>A</sub> receptors, alpha1 noradrenergic neurons located in the locus coeruleus. The latter neurons activate glutaminergic neurons, which are inhibited via m5Glu receptors by the glutaminergic neurons of the “mood center”, and they also inhibit via NMDA receptors 5-HT<sub>1A</sub> serotonergic neurons located in the medial raphe nucleus. Serotonergic neurons activate GABAergic neurons, which inhibit via GABA<sub>A</sub> receptors alpha1 noradrenergic neurons, which activate glutaminergic neurons. In the center of the circadian rhythm, noradrenaline and serotonin have alternating levels during the course of the day: serotonin is preponderant during the night and noradrenaline during the day [23]. In the hypothalamus, CRH-containing neurons with a high activity transmit a strong activating impulse via CRH<sub>1</sub> receptors to glutaminergic neurons, which in depressive states, strongly inhibit via m5Glu receptors 5-HT<sub>1A</sub> serotonergic neurons located in the brainstem “mood center” [23]. CRH-containing neurons located in the hypothalamus also activate GABAergic neurons, which inhibit

via GABA<sub>A</sub> receptors, hippocampal D<sub>2</sub> dopaminergic neurons. D<sub>2</sub> dopaminergic neurons, with a high activity in mania and with a weak activity in depression, activate glutaminergic neurons which inhibit via NMDA receptors 5-HT<sub>2A</sub> serotonergic neurons [18]. The latter neurons activate, via 5-HT<sub>2A</sub> receptors, hippocampal GABAergic neurons (Figure 1). Nicotinic cholinergic neurons, via alpha4beta2 nACh receptors, activate D<sub>2</sub> dopaminergic neurons. Neuropeptide Y-containing neurons located in the dentate gyrus inhibit, via NPY<sub>1</sub> receptors, GABAergic neurons, and substance P-containing neurons activate via NK<sub>1</sub> receptors GABAergic neurons. Finally, hippocampal GABAergic neurons inhibit alpha1 noradrenergic neurons located

in the brainstem center of the circadian rhythm, and hippocampal glutaminergic neurons inhibit 5-HT<sub>1A</sub> serotonergic neurons located in the brainstem center of the circadian rhythm [23] (Table 1).

### Treatment of Bipolar Disorder

For the treatment of bipolar disorder, second-generation antipsychotic drugs such as risperidone, olanzapine, quetiapine or aripiprazole or mood-stabilizing drugs are available [24]. Among the mood-stabilizing drugs, lithium can prevent the recurrence of depressive or manic symptoms in 30% of patients. Besides, the newer mood-stabilizing drugs valproate and lamotrigine exert a good



**Figure 1:** Neuronal pathways, classical neurotransmitters and neuropeptides involved in bipolar disorder. 5-HT: Serotonin; Ach: Acetylcholine; DA: Dopamine; CRH: Corticotropin-Releasing Hormone; GABA: Gamma-Aminobutyric Acid; Gal: Galanin; Glu: Glutamate; NA: Noradrenaline; NPY: Neuropeptide Y; SP: Substance P. The following subreceptors are indicated: alpha4beta2 nACh: alpha4beta2 nACh, a subreceptor of the nicotinic cholinergic receptor; CRH<sub>1</sub>: the CRH<sub>1</sub> receptor, a subreceptor of the corticotropin-releasing hormone receptor; GABA<sub>A</sub>: GABA<sub>A</sub> receptor, a subreceptor of the GABA receptor; GABA<sub>B</sub>: GABA<sub>B</sub> receptor, a subreceptor of the GABA receptor; 5-HT<sub>1A</sub>: 5-HT<sub>1A</sub> receptor, a subreceptor of the serotonergic receptor; 5-HT<sub>2A</sub>: 5-HT<sub>2A</sub> receptor, a subreceptor of the serotonergic receptor; D<sub>2</sub>: D<sub>2</sub> receptor, a subreceptor of the dopaminergic receptor; m5Glu: m5Glu receptor, a subreceptor of the metabotropic glutaminergic receptor; NK<sub>1</sub>: the NK<sub>1</sub> receptor, a subreceptor of the tachykinin receptor; NMDA: NMDA (N-methyl-D-aspartate) receptor, a subreceptor of the ionotropic glutaminergic receptor; NPY<sub>1</sub>: NPY<sub>1</sub> receptor, a subreceptor of the neuropeptide Y receptor.

Brain area	Neural network	Afferent or efferent neurons
Circadian rhythm center of the brainstem	Noradrenergic neurons from the locus coeruleus and serotonergic neurons from the medial raphe nucleus have alternating levels during the course of the day. Alpha1 noradrenergic neurons activate glutaminergic neurons which, via NMDA receptors, inhibit 5-HT <sub>1A</sub> serotonergic neurons. The latter neurons activate GABAergic neurons which, via GABA <sub>A</sub> receptors, inhibit alpha1 noradrenergic neurons.	<ul style="list-style-type: none"> <li>GABAergic neurons from the "mood center" in the brainstem inhibit GABAergic neurons via GABA<sub>B</sub> receptors.</li> <li>Glutaminergic neurons from the "mood center" in the brainstem inhibit glutaminergic neurons via m5Glu receptors.</li> </ul>
"Mood center" of the brainstem	Alpha1 noradrenergic neurons activate glutaminergic neurons which, via m5Glu receptors, inhibit 5-HT <sub>1A</sub> serotonergic neurons. The latter neurons activate GABAergic neurons which, via GABA <sub>B</sub> receptors, inhibit alpha1 noradrenergic neurons.	<ul style="list-style-type: none"> <li>Glutaminergic neurons from the hypothalamus which are activated by CRH neurons inhibit 5-HT<sub>1A</sub> serotonergic neurons via m5Glu receptors.</li> </ul>
Hypothalamus	Neurons containing corticotropin-releasing hormone activate GABAergic and glutaminergic neurons via CRH <sub>1</sub> receptors.	<ul style="list-style-type: none"> <li>GABAergic neurons inhibit D<sub>2</sub> dopaminergic neurons in the hippocampus.</li> <li>Glutaminergic neurons inhibit 5-HT<sub>1A</sub> serotonergic neurons in the "mood center" of the brainstem.</li> </ul>
Hippocampus	D <sub>2</sub> dopaminergic neurons activate glutaminergic neurons, which via NMDA receptors inhibit 5-HT <sub>2A</sub> serotonergic neurons. The latter neurons activate GABAergic neurons which, via GABA <sub>A</sub> receptors, inhibit D <sub>2</sub> dopaminergic neurons.	<ul style="list-style-type: none"> <li>Nicotinic cholinergic neurons activate D<sub>2</sub> dopaminergic neurons via alpha4beta2 nACh receptors.</li> <li>Neuropeptide Y neurons from the dentate gyrus inhibit GABAergic neurons via NPY<sub>1</sub> receptors.</li> <li>Substance P neurons activate GABAergic neurons via NK<sub>1</sub> receptors.</li> </ul>

**Table 1:** Neural networks in the brainstem, hypothalamus and hippocampus in bipolar disorder.

therapeutic effect [25]. The mechanisms of action and the therapeutic effects of these prophylactic drugs will be explained.

### Second-generation antipsychotic drugs

Among the second-generation antipsychotic drugs, risperidone has a D<sub>2</sub> and 5-HT<sub>2A</sub> antagonistic effect with a higher affinity for the D<sub>2</sub> receptor than olanzapine [26]. Risperidone can improve manic symptoms and partly depressive symptoms. Olanzapine has as well a D<sub>2</sub> and 5-HT<sub>2A</sub> antagonistic effect with a greater affinity for the 5-HT<sub>2A</sub> receptor than risperidone. It improves as well affective symptoms. Quetiapine also exerts a D<sub>2</sub> and 5-HT<sub>2A</sub> antagonistic effect with an even greater affinity for the 5-HT<sub>2A</sub> receptor than olanzapine. It improves manic and depressive symptoms [26]. Aripiprazole has a partial agonism at the D<sub>2</sub> receptor, and also exert a 5-HT<sub>2A</sub> antagonistic and a 5-HT<sub>1A</sub> agonistic effect. It improves well manic and depressive symptoms. Bipolar disorder should be treated with monotherapy, although a combination of mood-stabilizing drugs with antipsychotic drugs is given. In bipolar mania, lithium or antipsychotic drugs should be administered, while lithium should be given preferentially. In bipolar depression, quetiapine should be given [27].

### Mood-stabilizing drugs

Lithium has been used as a mood-stabilizing drug for more than half a century, and it has a secure prophylactic effect [25]. Its mechanism of action can be described as follows: it reduces the activity of the excitatory neurotransmitters dopamine and glutamate, increases the inhibitory effect of GABA, reduces the oxidative stress and has a neuroprotective effect [25]. Among the mood-stabilizing antiepileptic drugs, valproate and lamotrigine will be pointed out [28]. Valproate is a mood stabilizer in bipolar disorder and mania. It inhibits GABA channels, enhances the presynaptic inhibitory effect of GABA and thus stabilizes dopaminergic neurons in the hippocampus [28]. Lamotrigine blocks voltage-gated sodium channels and alpha4beta2 nACh receptors and hence stabilizes dopaminergic neurons. Besides, it blocks NMDA receptors and weakly AMPA receptors [28].

### Conclusion

In this review, we describe the alterations of neurotransmitters and neuropeptides, acting at specific subreceptors in the brain regions (brainstem, hypothalamus, and hippocampus) involved in

bipolar disorder. The coherence between the pituitary-hypothalamic-adrenocortical axis and the brainstem and hippocampus is described. In bipolar disorder, if the susceptibility genes are present, stress can enhance depressive or manic symptoms. Neural networks in the above-mentioned brain areas are described. The main and secure treatments for bipolar disorder are lithium, mood-stabilizing drugs and second-generation antipsychotic drugs. The neurotransmitters involved and the subreceptors, on which these prophylactic drugs interfere, are indicated in the neural networks described.

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