Neuroendocrine Stress System in Bipolar Disorder

Mario F. Juruena, Anthony J. Cleare, and Allan H. Young

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Abstract Hormones have a crucial part in the progress and manifestation of a wide variety of different behaviors. The main influence of the neuroendocrine system on behavior is its action on the neurobiology of neuropsychiatric disorders and its relationship with the pharmacodynamics of medicines. Of all the neuroendocrine axes, the hypothalamic-pituitary-adrenal (HPA) axis has been the most extensively studied. There is evidence that disturbance in the HPA axis, the primary stress hormone system, could increase treatment resistance and relapse, worsen illness outcome, and cause cognitive deficits. Glucocorticoids mediate their actions in negative feedback binding in two different cytoplasmatic receptors described as mineralocorticoid receptors (MRs) and glucocorticoid receptors (GRs). Different psychopathologies underlying bipolar disorders are supposed to involve persistent dysfunctions in the expression and role of both MR and GR in the hippocampus. We review and analyze the evidence related to the correlation between bipolar disorders and the consequences and impact of stressful life events on the HPA axis, exploring

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the importance of these findings in bipolar disorders and as potential new targets for treatment.

Keywords Cortisol · Glucocorticoid receptors (GRs) · Hypothalamic-pituitary-adrenal (HPA) axis · Mineralocorticoid receptors (MRs)

1 Introduction

A central problem of diagnosis in psychiatry is that the current nosology systems for mental disorders are based almost entirely in descriptions of symptom-based categories (phenomenology). A comprehensive categorical classification described different clinical disorders, but there is no evidence of a biomarker that differentiates the different subtypes in the bipolar spectrum. Different psychiatric illness can manifest the same clinical symptoms, and the same mental illness can demonstrate itself differently in distinct or in the same patient. A future system of nosology criteria, in which etiology and neurobiology could be incorporated to diagnosis criteria would provide a more accurate pathway to precision psychiatry. The connection between stressful life events and mental disorders illness is a robust illustration of an area of study that can be better understood from such an integrative perspective (Ray 2004).

It is believed that disturbance of the stress hormone system (mainly, the hypothalamic-pituitary-adrenal axis) may cause cognitive impairment and make the depressive symptoms worse in bipolar disorder. Research has shown (Watson et al. 2004), that HPA axis dysfunction may predict an inadequate clinical response to drug treatment (Young et al. 2004; Juruena et al. 2009). Current studies demonstrate that the brain and its cognitive processes work in extraordinary synchrony with other bodily systems. Consequently, it is now possible to conceptualize a brain-body-mind complex when it is known that the three systems – neurological, endocrinological, and immunological – have receptors in crucial connections that can receive influences (by messenger molecules) from each of these systems. Body-mind interaction, an explicit functioning of the brain, is critical to maintaining homeostasis and well-being (Ray 2004). Today, it is widely accepted that psychological stress can alter an individual's internal homeostatic state.

In an acutely stressful event, several adaptive homeostasis and allostasis reactions may happen, including enlargement of the adrenal gland, increasing the release of hormones, mainly cortisol. Repeated stress may precipitate a psychiatric illness in genetically vulnerable individuals if this homeostasis is interrupted. Psychosocial stressful events can change neurophysiology and performance and influence the adaptation process (McEwen 2001). As experiences change our central nervous system, cognition can modify our brain. This neuropsychological process in the brain is an action in favor of neural and mental health. Genes, early stress, adulthood

experiences, and stressful events contribute in the way all these may request the body to "pay the price" – or the "allostatic load" (McEwen 2001). These discoveries in current neuroscience and their consequences are essential for diagnosis and treatment of bipolar disorders (Juruena et al. 2007).

In a diagnosis point of view, the investigation has mainly concentrated in unipolar depression; just a few projects have studied biomarkers in well-defined and different subtypes of depressive and bipolar disorders. Several research projects and clinical trials have studied different subtypes of depression in the same group, in an explicit limitation of these projects that have not considered even phenomenology differences. It has been studied the differences between major depressive disorder and bipolar depression, mainly concerning their psychopathology, not correlating and stratifying biomarkers.

Cognitive impairment in bipolar patients is common (Robinson et al. 2006). Neuropsychological deficits on neurocognition (e.g., working memory, spatial memory and executive function) are also seen in family members of bipolar patients (Arts et al. 2008) and bipolar subjects in remission without residual symptoms (Thompson et al. 2005). Cognitive damages increased the severity significantly and decreased remission, recovery, and resilience (Burdick et al. 2010).

2 Endocrine Axis

The neuroendocrine system has a central importance in the evolution and manifestation of a wide variety of behaviors. Hormones have a probable influence on the neurobiology of neuropsychiatric illness and psychopharmacology medications, mainly in affective disorders.

Between all the neuroendocrine axes, the hypothalamic-pituitary-adrenal (HPA) axis is defined as the central stress axis and has been better studied. The HPA axis has a crucial function in responding to stressful events, but also any internal stimulation, including emotional stressors. Dysfunction of the stress axis has been described in patients with bipolar disorder. Also, the fundamental role of stressful events as a precipitant of manic and depressive episodes in vulnerable subjects is clear evidence. Dysfunction of the HPA axis is associated with fluctuations in the ability to circulate glucocorticoids (GCs) to exert their negative feedback on the release of hormones on the HPA axis by binding to mineralocorticoid receptors (MRs) and glucocorticoid receptors (GRs) in HPA axis (Juruena 2014), as shown in Fig. 1.

2.1 Regulation of the Hypothalamic-Pituitary-Adrenal Axis

The activity of the HPA axis is regulated by the secretion of corticotropin-releasing hormone (CRH) and arginine-vasopressin (AVP) by the hypothalamus, which activates the secretion of the adrenocorticotropic hormone (ACTH) by the pituitary,

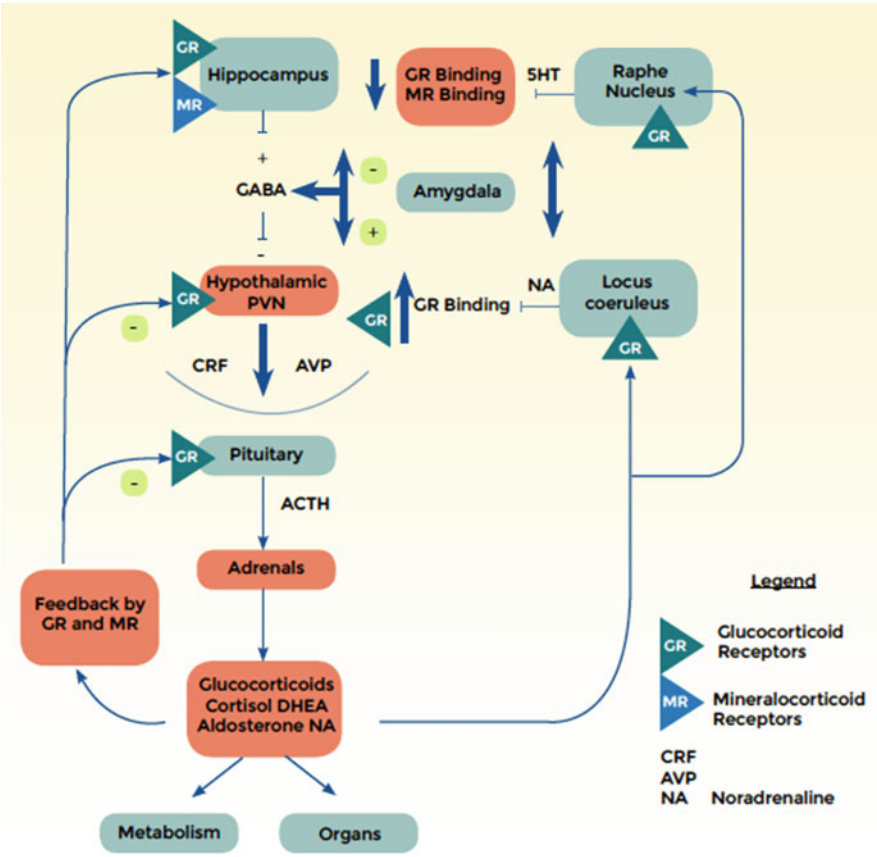

Fig. 1 Representation of the HPA axis. It summarizes the negative (−) feedback of hormones binding in GR and MR. The system includes essential areas of the limbic system, amygdala, hippocampus, locus coeruleus, raphe nucleus, and their relation via noradrenaline (NA) and serotonin (5HT), with adrenal hormones and GR/MR. It is adapted from Juruena et al. (2017). Illustrations are courtesy of Romayne Gadelrab

which ultimately stimulates the secretion of GCs by the adrenal gland (McEwen 2004). GCs then bind with their receptors in several target structures, mainly brain areas responsible for regulating the HPA axis, impacting on the negative feedback inhibition of ACTH (since the pituitary) and CRH (since the hypothalamus) secretion (Juruena 2014). Although GCs control the function of virtually all tissues in humans, the neurophysiological action of these neurohormones is mainly the regulation of metabolism. The GCs have significant immunosuppressive and/or anti-inflammatory actions (Rosenblat and McIntyre 2017). Several factors regulate the activity of the HPA axis. There is evidence of direct catecholaminergic, serotonergic, and dopaminergic innervation in CRH-producing neurons in the hypothalamus; these and other neurotransmitters appear to influence the release of CRH (McQuade

and Young 2000). For example, serotonin exerts a stimulating influence on CRH through the 5-HT1A, 5-HT1B, 5-HT1C, and 5-HT2 receptors. The norepinephrine (NE) has an adjustable action; NE is stimulating at lower doses via alpha-1 receptors and has inhibition effect at higher doses via B-receptors (Yohn et al. 2017).

2.2 The Glucocorticoid Receptor (GR)

The steroid hormones (GCs, testosterone, mineralocorticoid, estrogen) are fat-soluble molecules that disseminated through the lipid-protein membrane. Different from the neurotransmitter's receptors, which are located on the lipid-protein membrane, receptors for steroid hormone are situated inside the cytoplasm. In response to coupling to these hormones, the stress hormone receptors migrate to the nucleus, where they induce some genes via binding to precise hormonal response elements (HREs) in respective controlling areas (Holsboer and Barden 1996; Juruena 2014).

The mineralocorticoid receptor (MR) has a higher affinity for corticosteroids and is considered to regulate circadian oscillations in these corticosteroids, especially in ACTH release in the progressive daytime fall in cortisol secretion. De Kloet et al. (1998) clarified that glucocorticoid receptor (GR) activation is crucial for regulating the HPA axis negative (−) feedback when GCs are higher in response to a stressful event and/or in a physiological higher activation point and also demonstrated that the MR has an essential function in the balance of MR/GR.

As said earlier, in the nucleus to cytoplasmic traffic model of receptor action, as detailed in Fig. 2, the GR – in its inactive configuration – primarily exists in the cytoplasm in association with molecular chaperone proteins, including numerous proteins (e.g., HSP56, HSP90).

After being coupled to the steroid, the receptor experiences a conformation alteration (initiation), itself since the molecular HSP protein composite, and migrate, then modulating negatively and/or positively to alter the gene transcription, coupling with glucocorticoid response elements (GREs). The GR then reprocesses to the cytoplasm. Subsequently, it works with a transcription factor regulated by the ligand by coupling to GREs (de Kloet et al. 1998; Juruena et al. 2003).

Evidence confirmed the GR has a lower affinity, but a with a stronger binding to glucocorticoids; GR is also significantly reactive to alteration in cortisol levels. Although it is considered that MR may be involved in the tonic inhibitory activity on the HPA axis, GRs seem to "shut down" cortisol production in times of stress (de Kloet and Reul 1987; de Kloet et al. 1998). Several research groups have suggested that the hyperreactivity of the stress axis in a depressive episode that could be associated with a dysfunction of GR at the amygdala, hippocampus and limbic system level. These dysfunctions result in a decrease in receptors and/or resistance to GCs. Several findings in depressive patients confirmed GR dysfunction. Most notable is that in melancholic depressive episodes, subjects do not exhibit many of the symptoms of an excess of GCs, despite the frequent incidence of higher

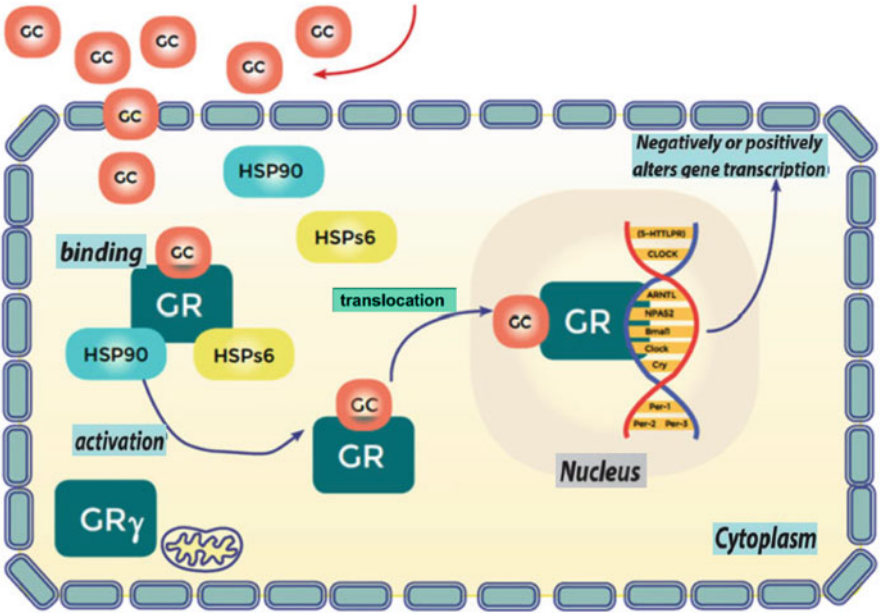

Fig. 2 Diagram of the glucocorticoid receptor (GR) stimulation; this receptor exists at the cytoplasm with chaperone proteins with numerous proteins (HSP56, HSP90). Glucocorticoid (GC) binds as GR ligands. Then the GR experiences an alteration disconnected from the HSP and migrated to the cell nucleus from the cytoplasm, modulating negatively or positively to alter the gene transcription. Adapted from Juruena 2014. Illustrations are courtesy of Romayne Gadelrab

cortisol, indicating that the peripheral receptors could be dysfunctional or downregulated in depression (Young et al. 2004; de Kloet et al. 1998).

The evidence confirmed that the GR is crucial to regulate the activity of the HPA axis, mainly in depressive subjects if glucocorticoids do are not leading to negative feedback in a scenario of hyperactive stress axis and hypercortisolism. Some data have concluded that the decreased GR function in depression could be reversed by the treatment that could be modified and improve the balance of GR/MR function (Holsboer and Barden 1996).

2.3 Mineralocorticoid Receptors (MRs)

MRs in the central nervous system are related to regulating the release of stress hormone and in the regulation of multifaceted behavior, such as sleep, emotion, and memory. In human, the function of MR in the neurobiology of stress and neuropsychiatric illness has not been sufficiently characterized. However, new studies found potential options for new psychopharmacotherapy via regulation of MR function (Geddes and Miklowitz 2013).

Significant research in animals concluded that MR at the hippocampus regulates the inhibition of limbic system over the HPA axis, in baseline or after induced stress (Reul et al. 2000).

Preclinical research using MR and/or GR antagonists have verified that MR stimulation is needed and enough to preserve lower basal corticosterone release in animals in a diurnal assessment. In contrast, GR stimulation is needed to limit corticosterone release during the daily peak and/or in stress. Nevertheless, during the diurnal peak or recent stress, MR stimulation induced an essential function in enabling the GR and MR activity of HPA axis function of glucocorticoids (Pace and Spencer 2005; Ratka et al. 1989; Spencer et al. 1998). Some preclinical studies antagonizing MR, with spironolactone, demonstrated anxiolytic properties in distinction to antagonists of GR (Smythe et al. 1997). Nevertheless, they demonstrated that both MR and GR antagonists stopped the impact of stress that induced anxiogenic properties in the high plus-maze paradigm (Calvo and Volosin 2001). The author determined that MR and GR are autonomously related to chronic glucocorticoid regulation of the anxiogenic reaction impact by restraining. Dysfunction of glucocorticoid receptor was described in disorders related to chronic stress. To clarify the function of different receptors, it should be studied, mainly related to memory function and stress-related events. A study described that the MR is upregulated and remains in this state after the treatment with antidepressant during 6 to 9 weeks, whereas GR proceeds to baseline levels (Mason and Pariante 2006). Spironolactone, an MR antagonist, was administrated 25 mg/kg, in the previous corticosteroid treated animals during 7 days. The authors described they decreased immobility in a forced swimming test and had a better performance in a new object recognition test. In summary, chronic glucocorticoid-induced and start several depressive related symptoms, and decrease MR expression in critical areas, as the hypothalamus and hippocampus. MR antagonist confers an antidepressant effect in chronic corticosteroid-pretreated individuals.

Up till now, just some studies described MR activity in severe mental illness and its relation to HPA axis and other brain structures. The first description was in postmortem research suicide subjects that confirmed lower MR messenger RNA in the hippocampus in relation to healthy controls (Lopez et al. 1998). To test the hypothesis that MR function is decreased in depression, a study used an antagonist (spironolactone) in a clinical trial to assess in depressed subjects with lower MR function. Paradoxically, a higher function was observed with a higher release of cortisol and ACTH after an MR antagonist is used in mildly depressed patients (Young et al. 2003). We can hypothesize that increased MR function may indicate resilient function to protect neurodegeneration in depression. Therefore, MR may prevent central nervous system from apoptosis and keep resilient mechanisms increasing serotonergic function (Crochemore et al. 2005; Cowen 2002; McAllister-Williams et al. 1999, 2001; Porter et al. 2004).

The spironolactone demonstrates a significant increase of cortisol release without circadian differences in the administration. Elizabeth Young et al.'s (1998) research concluded that the vital function of MR in HPA axis activity in human is at the peak and/or the nadir of the circadian rhythm (Young et al. 1998). Additionally, the

neurophysiological alteration of HPA axis secretion in man during sleep onset in the non-REM phase was described to be blocked in the acute administration of MR antagonists (Born et al. 1997; Born and Fehm 1998). Several research projects have investigated the MR antagonists' impact on neuroendocrine hormone release and have generated different results (Dodt et al. 1993; Steiger et al. 1993, and Wiedemann et al. 1994).

The benzodiazepine receptor agonist alprazolam can block the stimulatory effect of MR antagonists upon HPA axis activity, probably on the GABA receptors on the hypothalamus and hippocampus (Grottoli et al. 2002).

Some research indicated that activation of MR increases the time of slow-wave sleep and canrenoate (an active metabolite of spironolactone) and decreases the time of slow-wave sleep (Born et al. 1991, 1997). However, other studies demonstrated that MR antagonism reduced REM sleep phase but did not change the time of the slow-wave sleep (Wiedemann et al. 1994). Kuningas et al. (2007), in elderly patients, found a higher prevalence of depression in patients carrying the MR-I180V polymorphism. Buckley and Schatzberg (2005) suggested a decrease in memory in healthy elderly could be improved, increasing the slow-wave sleep.

2.4 Molecular Mechanisms for Resistance of Glucocorticoid Receptors

Numerous studies have evaluated GR in depressive, bipolar, and schizophrenic patients. An autopsy of the central nervous system, in a sample of suicide patients with a history of depressive symptoms, found hippocampus decreased gene expression of GR/MR balance (Lopez et al. 1998). Therefore, the stress axis could be dysfunctional in bipolar and schizophrenic patients, and the impairment in the HPA axis could lead to different neuropsychiatric disorders.

Evidence shows that chronically high levels of cortisol can lead to receptor dysfunction and corticosteroid resistance, related to inflammation. Probably the chronic increase in cortisol released could develop GR resistance in bipolar disorder (Holsboer and Barden 1996). In patients with treatment response, high cortisol levels decreased, and lymphocyte resistant to dexamethasone returns to normal range. We can argue that treatment-resistant depression could also be related to glucocorticoid steroid resistance. However, high levels of corticosteroids and receptor resistance may not happen at the same time, and it could be that different subtypes of activation may lead to different courses in different types of bipolar disorder according to HPA axis activity (Holsboer and Barden 1996; Zobel et al. 2001).

Although the information presented here provides substantial evidence that there is resistance to glucocorticoids in depressive patients, and studies suggested that normal activity to cortisol in depression could be preserved peripherical. Mainly, it has been shown that depressed patients with severe metabolic syndrome, as in some patients with higher cortisol levels with Cushing's syndrome after prolonged treatment with a corticosteroid. Probably intra-abdominal receptors can maintain their affinity to cortisol while brain receptors are dysfunctional. Corroborating it, some

data showed decreased bone mineral concentration in patients with depression, as well as association with bone loss (Checkley 1996; Young and Juruena 2018).

3 Abnormalities of the HPA Axis in Depression

In melancholic depression, there is evidence of increased activation of the HPA axis, increased release of ACTH and CRH, and increased cortisol levels, mainly post-challenge tests. On the other hand, the first studies with patients in a depressive episode with atypical features with inverted vegetative symptoms demonstrated reduced cortisol and lower HPA activity when compared with controls. However, most of the studies have not differentiated this depressive subtype from healthy controls (Juruena et al. 2018). The same dysfunction observed in one or recurrent melancholic depressive episodes may also be present in bipolar patients in mixed, manic, hypomanic, and/or depressive episodes (Juruena et al. 2011; Valiengo et al. 2012), see Fig. 3.

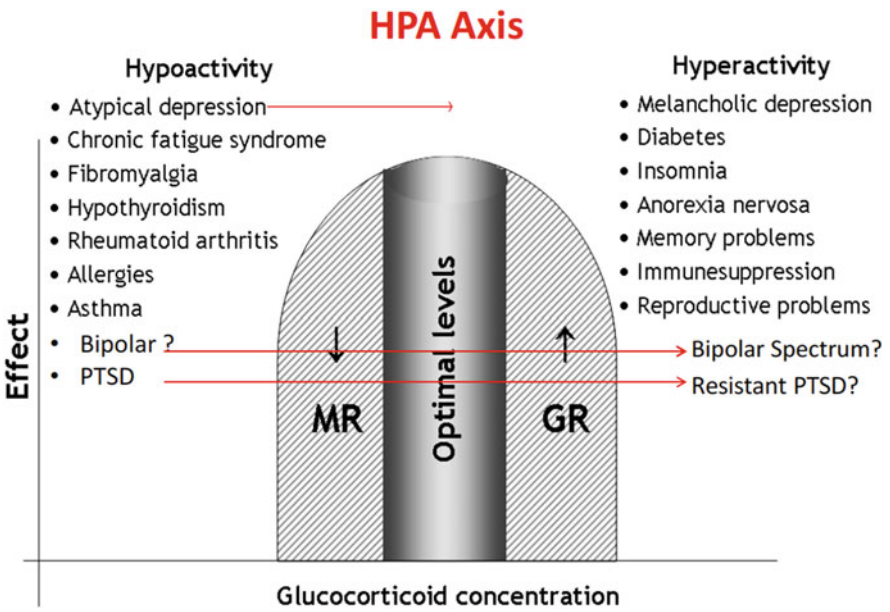

Fig. 3 The HPA axis dysfunction induces changes in the activity of GCs on the MR and GR and in the (−) feedback impacting on the release of HPA axis hormones. An impaired (−) feedback, leading to increased GCs, as in melancholic depression, diabetes (mainly type II), eating disorders (e.g., anorexia), and sleep disorders (e.g., insomnia). The hypoactivation of the HPA axis may increase the negative (−) feedback, in subjects with atypical depression (or normal activation), seasonal affective disorders, post-traumatic stress disorder (PTSD), fibromyalgia, and chronic fatigue syndrome. Bipolar and PTSD depending on the course could be related to lower or higher activity of the HPA axis. Adapted from de Kloet et al. (1998), Juruena et al. (2018), Palma et al. (2007), Gold and Chrousos (2002), and Young and Juruena (2018)

Most of the patients in these affective disorders' episode have the following abnormalities (Dallman 1984; Nemeroff et al. 1984):

- Augmented levels of cortisol: in the plasma, saliva, urine, and cerebrospinal fluid (CSF).
- Increased response of cortisol to ACTH.
- It is increased the pituitary and adrenal glands.

Several published data in the last years have confirmed that the increased HPA axis activity could be understood as an endophenotype of vulnerability that reacts to stressful events increasing the cortisol levels with an impairment in the negative feedback in depressive patients associated with different subtypes of depressive episodes (Juruena 2014):

- The subtype of the depressive episode, course, comorbidity, and severity of current episode
- The epigenetic and the genotype
- The history of childhood trauma (abuse and neglect)
- The presence or not of resilience

Adrenal gland hypertrophy has been found in depressed patients. The observation of adrenal hypertrophy in depressed episodes probably elucidates that the cortisol increase, stimulated by CRH, is analogous to the enlarged adrenal gland to compensate the blunted ACTH to compensate CRH levels, generally seen in depressive episodes (Dallman 1984; Nemeroff et al. 1984; Juruena 2014).

In depressive episodes, an enlargement of the pituitary volume was observed, which can be considered a biomarker of excessive stimulation of the HPA axis. Patients with psychosis have also been related to enlargement of the pituitary gland and increased activation of HPA axis. A decreased volume of the pituitary gland in psychotic patients may be related to recurrent episodes leading to hyperactivity of the stress axis (Axelson et al. 1992).

In general, changes in the HPA axis are described in patients with chronic depression and with severe depressive episodes, such as psychotic and treatment-resistant depression. Also, if these dysfunctions are related to the current episode, the tendency is for them to improve with the response and/or remission of the more recent episode of depression (Holsboer and Barden 1996).

Numerous data from several different research topics have described the impact of depressive episodes in brain structures, such as the amygdala, insula, hippocampus, and HPA axis. These data have described an increased release of CRH and AVP, at the hypothalamus, that could stimulate the pituitary and adrenal activity. In addition, CRH levels in the CSF are augmented in depression, mainly in untreated depressive episodes. In suicide victims, fewer CRH receptors were found in the frontal cortex, thought to be a down-regulatory response to higher CRH release. Several studies described that elevated CRH might influence depressive episode with inverted vegetative symptoms (Juruena and Cleare 2007; Juruena et al. 2018), such as:

- Diminished libido
- Diminished appetite
- Psychomotor changes
- Sleep disorders

Regarding neurobiological markers, cortisol is considered one of the primary mediators of allostatic load (McEwen 2001). Several studies in bipolar disorder – and major depressive disorder – demonstrate dysfunction of the HPA axis, with the maintenance in high levels of corticosteroids even in phases of remission of the disease, due to possible negative impaired feedback in the HPA axis (McEwen 2001). Also, abnormalities in axis regulation can predict depressive and manic relapses (Holsboer and Barden 1996; Varghese and Brown 2001; Vieta et al. 1999). It could be considered that the reduction of resilience, with the repetition of episodes and the increase of stressors in the progression of the disease, might be related to the dysfunction of the HPA axis (Juruena 2014).

Recently, several data described that the neurobiology of psychotic depression included significant and higher HPA axis activity compared with depression without psychotic symptoms (Schatzberg et al. 1983; Keller et al. 2017). These data describe the increased activity of the stress axis in psychotic depression, which is related to increased concentration of cortisol. Increased cortisol activity, particularly modifying the lowest point on the curve, is related to the severity of psychotic depression. Probably this comorbidity of psychosis and depression gravely harms the neuroendocrine system related to stress, comparable to Cushing neuroendocrine effects, and the imbalance in the activation of MR and GR (Schatzberg et al. 2014).

3.1 Impact of Stress on Bipolar Disorders

The progression of mood disorders, characterized by the recurrence of acute episodes, can be compared to models of sensitization to stress and models of electrophysiological kindling, as reviewed by Post (2007). This phenomenon of accelerating episodes was initially described by Kraepelin in 1899, suggesting that psychosocial stressors often initiate early episodes, while new recurrences may become autonomous and independent of environmental triggers (Post 2007, 2010).

Specifically, the progression of bipolar disorders has been linked to an increase in "allostatic load," which may help to explain the cumulative medical load associated with recurrent episodes of mood. It is believed that bipolar disorder patients are chronically exposed to stressful events and need to activate mechanisms to deal with them. Chronic activation of allostatic mechanisms (e.g., activation of the HPA axis and subsequent reduction in cortisol levels back to their basal levels) can lead to a reduction in resiliency mechanisms. This process can ultimately establish a vicious cycle progression, in which patients become more vulnerable to stress and triggers for new episodes as the disease progresses; see Table 1.

Table 1 Progression of bipolar disorder

A) Stressful events can act as triggers for acute mood episodes (mainly in the onset and early phases of the disorder), activating the stress axis and inducing the release of high levels of glucocorticoids in the circulation
B) High levels of cortisol can, in the long run, induce cell dysfunction, which may result in cell death (apoptosis) or reorganization of dendrites in the case of neurons
C) This reorganization can ultimately lead to significant neuroanatomical changes, such as an increase in the volume of the amygdala and a decrease in the volume of the hippocampus and the prefrontal cortex
D) These changes, consequently, lead to a decrease in the ability to deal with stressors (less resilience) and, therefore, greater vulnerability to the occurrence of new acute episodes of mood

Different studies have reported abnormalities in cortisol levels in depressive and bipolar episodes (Havermans et al. 2011; Juruena et al. 2003). Specifically, a large proportion of patients are resistant in the suppression of the HPA axis after a dexamethasone suppression test (DST). Also, they have increased corticosteroid release, irrespective of the stage of the disease (Watson et al. 2004; Sher et al. 2006). These observations indicate damage in the negative feedback loop of the HPA axis, which persists even after the remission of acute depression. Patients with abnormalities in the HPA axis have more vulnerability to recurrent episodes and relapses in unipolar depressive and bipolar episodes (Zobel et al. 2001; Vieta et al. 1997).

In addition to the already described HPA axis alterations in depressive episodes, studies suggest that such dysfunction also occurs during manic, hypomanic, and mixed episodes. Previous research using dexamethasone indicated a change in the release of glucocorticoids in manic episodes in mixed characteristics (Evans and Nemeroff 1983; Swann et al. 1992). A study that used the dexamethasone/CRH (DEX/CRH) test in patients with acute mania an augmented suppression to the DEX/CRH test was reported when compared to healthy subjects; these dysfunctions could also be observed after treatment in response and/or remission in manic patients (Schmider et al. 1995). Likewise, the CRH test in bipolar patients, during symptoms remission, could predict new episodes of mania. Studies with the release of cortisol from the HPA axis reported alterations in the stress axis flow during manic episodes. For example, one study found that plasma cortisol was significantly increased at night in manic patients compared to controls (Linkowski et al. 1994). Bipolar in different episodes – mania and/or hypomania, depression and/or euthymia – had high levels of cortisol when compared to controls, with no differences between patients (Cervantes et al. 2001). The deficiency in the negative feedback at different levels of the central neuroendocrine system in regulating circulating cortisol levels results in a mechanism that leads to an exaggerated increase in cortisol levels during stress and decreases the HPA axis' ability to resume these to baseline levels (Tatro et al. 2009). The increased cortisol, therefore, can have significant long-term consequences in patients with bipolar disorders, since glucocorticoids play essential roles in the process by which allostatic mediators interact with neurotransmitter systems and brain peptides (McEwen 2004; Juruena et al. 2017). In addition to altering neuroplasticity, the dysfunction of the stress axis can impact on different levels of the

daily rhythm, e.g., cycle vigil/sleep. Most of these parameters have already been correlated with the neurophysiology of bipolar and depressive episodes (Murray and Harvey 2010).

In bipolar patients, there is evidence that points to high levels of cortisol regardless of the current mood state (Deshauer et al. 2003; Cassidy et al. 1998; Schmider et al. 1995; Linkowski et al. 1994). Patients in a first manic episode without treatment showed decreased plasma cortisol levels compared to controls, with high levels positively correlated with the presence of irritability (dysphoria) and elevated mood (euphoria) correlated with lower levels of cortisol (Valiengo et al. 2012). Also, the long-term assessment of cortisol levels did not show significant differences, being elevated only in patients with a later age of onset of the disease, after 30 years (Manenschijn et al. 2012). The rise in cortisol levels has also been reported as a biomarker for vulnerability to bipolar disorders in family members of bipolar patients (Ellenbogen et al. 2011).

3.2 Impact of Mediating Factors on the HPA Axis

The study of the functioning of the HPA axis in bipolar disorders presents sometimes inconsistent results. While some studies point to abnormalities comparable to those seen in depression, especially in patients in a current mixed episode, others do not indicate any change (Schlesser et al. 1980; Swann et al. 1992; Evans and Nemeroff 1983). There is evidence of increased activity of the stress axis in patients with a history of suicidal behavior. However, normal HPA axis function in bipolar patients without a past of suicide behavior, regardless of demographic factors, current episode of mood, severity, and course disease (Kamali et al. 2012), suggests that this could represent a marker for this subgroup of subjects.

The serotonergic system mediates the core symptoms of severe bipolar patients, e.g., aggressivity, impulsivity, and suicidal behavior. Also, significant evidence are connecting the serotonergic neurons (raphe nucleus), the HPA axis, the amygdala, and the hippocampus; see Fig. 1. Therefore, one hypothesis is that in the neurobiology of bipolar is based in the dysregulation of the HPA axis via disturbances in the serotonin neurons, in which the stress axis appears to demonstrate decreased negative feedback and consequently increased cortisol released, associated with reduced serotonergic neuron activity. Thus, the interaction between these systems, required in the regulation of the stress response, seems to be altered (Juruena et al. 2017; Yohn et al. 2017).

Early life stress (ELS), especially maltreatment, abuse, and neglect, seems to be an essential factor of vulnerability for bipolar patients. Other susceptibility factors, as unbalanced parental relations as epigenetic factors, are also important (Juruena et al. 2015; Aas et al. 2016; Etain et al. 2013). In bipolar disorders, several changes in the central nervous system are related to emotional control, response inhibition, and autobiographical memory, mainly the limbic system prefrontal regions, amygdala, and hippocampus. As described the HPA axis activity and neurotransmitters have a

crucial function in these brain areas for emotional control and neuropsychological purposes (Watson et al. 2006; Wingenfeld 2010).

Bipolar and unipolar patients had been compared, and no significant differences between patients and healthy controls in the history of physical abuse were found. History of early life stress did not differ between bipolar and unipolar either (Watson et al. 2007).

Different subtypes of abuse and emotional neglect, although less studied, present significant evidence of influencing psychopathology and neuroendocrine systems. In studies carried out in animal models, it was observed that the sensitization of the stress system HPA axis occurred in reaction to different forms of stressful life events (Ladd et al. 2004). Also, data assessing the history of maltreatment, such different subtypes of abuse (e.g., physical, emotional, and sexual abuse) and neglect are significant predictors of severe affective psychopathology in adulthood (Brown et al. 2005). The history of emotional abuse demonstrated after a multiple logistic regression analysis as a significant factor for depression. Thus, these findings suggest that the history of emotional abuse is a significant risk factor involved in the pathogenesis of depression related to ELS (Martins-Monteverde et al. 2019).

The severity of early life stress may be another critical factor. Thus, physical neglect could play a role in activating the axis when present at lower levels, while its occurrence in greater severity may saturate the stress response, which can make it hypoactive. A study carried out with patients diagnosed with severe mood disorder showed a result suggestive of a similar relationship with emotional neglect, which correlated with the increased activation of the HPA axis when mild to moderate, but with no difference to healthy controls when this type of early stress was severe (Watson et al. 2007).

Several studies described patients where the relationship of ELS and stress axis in response to different types of stress impacts on the HPA axis, but results are somewhat controversial and varied, and not specific to bipolar disorders.

Studies with patients with a history of sexual abuse demonstrated increased activation of stress axis (Carpenter et al. 2007), and patients with a history of emotional abuse demonstrated hypoactivation and lower cortisol release (Carpenter et al. 2009; Feijo de Mello et al. 2007), and patients with history of emotional neglect and physical abuse also had decreased release of cortisol (Flory et al. 2009; Carpenter et al. 2007). Recently, a study suggests that flashbacks of traumatic memories as history of early life stress (e.g., abuse and/or neglect) are associated with female gender and increase the risk for affective disorders (e.g., depression, hypomanic and manic states; Haussleiter et al. 2020).

A study that compared bipolar and borderline personality disorder for influences associated with severity, early life stress, and cortisol found that borderline personality patients had a history of early life stress both overall and in subjects with emotional neglect, physical neglect, and emotional abuse than bipolar patients. The history of early life stress in patients with borderline personality and bipolar disorder was associated with decreased cortisol release. In this study the cortisol demonstrated contrary correlations in the history of sexual abuse, being a (−) correlation in bipolar patients and (+) correlation in borderline personality disorders (Mazer et al. 2019).

Overall, the risk factors of affective psychopathology are related to a complex interaction between several factors associated with the HPA axis and reflect the association of individual vulnerability with different subtypes of stressful life events for the progress of the neuropsychiatric illness. The assessment of possible biomarker related to HPA axis activity (e.g., cortisol) could be significant in precision psychiatry and diagnosis of bipolar disorders, such as the impact of a history of early stress and subsequent manifestations with late neuroendocrine changes. It remains unclear the extent to which such parameters may help with the difficulties of defining these disorders and whether they are different nosological entities or belong to the same continuum.

Although some drugs have been linked to changes in cortisol levels (Eroğlu et al. 1979; Venkatasubramanian et al. 2010; Heim and Nemeroff 1999; Watson et al. 2007), most of the clinical evaluation studies of the hormonal profile of the HPA axis are performed during the use of drugs usually prescribed for the condition studied (Valiengo et al. 2012; Juruena et al. 2006, 2010, 2013; Watson et al. 2007; Drevets et al. 2002).

Some studies, as mentioned earlier, found lowered cortisol levels in bipolar disorder contrasting with other evidence that described the increased activity of the HPA axis in bipolar disorder, regardless of the current affective state (Deshauer et al. 2003), during a mixed episode (Daban et al. 2005; Watson et al. 2004; Swann et al. 1992; Evans and Nemeroff 1983), in the presence of a history of suicidal behavior (Kamali et al. 2012), with the later age of occurrence of the first episode of the disorder (Manenschijn et al. 2012), or in the premorbid one evaluated in healthy family members. It has been described that these neuroendocrine changes may indicate a genetic vulnerability factor (endophenotype) for bipolar patients (Aydin et al. 2013; Duffy et al. 2012; Ellenbogen et al. 2011). However, in a clinical study evaluating patients in the first episode without previous treatment, decreased levels of cortisol were described, consistent with the finding of Mazer et al. (2019). In that study, cortisol measurements were correlated differently to mood presentation, according to Young Mania Rating Scale (YMRS): decreased cortisol in patients with higher scores of euphoria and increased cortisol in patients with higher irritability (Valiengo et al. 2012). Finally, subjects with normal cortisol release were described in another study (Schlesser et al. 1980) and also in bipolar patients without a history of suicide or younger age (Kamali et al. 2012; Manenschijn et al. 2012).

4 Factors Associated with an Endophenotype Increasing Vulnerability

We can understand better bipolar disorder if we can integrate an interaction of several influences, opening with the genotype, and including the environment experienced during childhood incorporating possible traumas, an individual

temperament that confers on the specific skills to cope and deal with different stress. The neuroendocrine system is vital to understand the neurobiology of bipolar disorder (Evans and Nemeroff 1983).

The central stress system is the HPA axis that plays a fundamental role in acute and chronic stressful events (Kendler et al. 2003). Interestingly, the stress in children, such as abuse and neglect, could lead to permanent pathophysiological dysfunctions that are similar to the neurobiology of depressive and bipolar patients. Personality traits and temperament also have an essential influence on the sensibility of stressors and life events. Likewise, a predisposition to live a negative feeling or to be socially repressed could be a consequence of emotional or neuroendocrine stressful life event (Rijsdijk et al. 2001; Kagan et al. 1987).

Animal and human studies indicated that early life stress could develop permanent dysfunctions, and this impairment in the HPA axis may increase the vulnerability to bipolar disorders. Persistently increased activity of the HPA axis has also led to more frequent relapses and treatment resistance (Holsboer and Barden 1996).

A wide variety of stressors have been shown to stimulate the HPA axis. For this reason, glucocorticoids have been described as key molecules to develop the stress reaction and severe physiopathology situations. The persistent release of glucocorticoids is a combination of recent current stress or an epigenetic vulnerability to increase the HPA axis activity and severe damages in central nervous structures (mainly the hippocampus), which are crucial for controlling this system and cognition (Davis et al. 2018; Gallagher et al. 2014, 2015).

There is a hypothesis that this damage, in turn, leads to a feedforward circuit in which permanent stressors stimulate the overproduction of GCs indeterminately (GC cascade). Due to the ability of higher release of GCs to alter cell metabolism, which could trigger a large number of recurrences in bipolar, it is considered that the overproduction of these hormones directly contributes to several behaviors and psychological damages related to frequent chronically stressful events in bipolar disorders (McEwen 2001; Watson et al. 2007). Despite the popularity of the cascade hypothesis, several studies described the release of excess of GCs, on the GR/MR can develop stressful reaction and trigger treatment-resistant affective disorders (Juruena 2014).

Thus defined, insufficient signaling by the GCs implies the endpoint of the GC function, the key research query is if GC's message is arriving appropriately to HPA axis after stressful life events. In some subjects with hyperactivity of HPA axis and high levels of GCs, there may be an insufficiency of these hormones if the reduced sensitivity to GC, in relevant target tissues, overcomes the excess of circulating hormone (Raison and Miller 2003; Sapolsky et al. 2000).

5 Conclusion

The observations described in this chapter provide support describing the fundamental influence of the HPA axis in the neurobiology of bipolar disorders; but it is essential to be clear that bipolar disorder is considered a complex and heterogeneous

clinical syndrome, as the current state of the evidence is insufficient to allow its characterization based on etiology or pathophysiology. To understand better the relationship between vulnerability and stressful environment in the genesis of bipolar disorder in adults, new research needs to study the several different influences in a comprehensive view of the interaction between genes and the environment. Such research will connect biological, epigenetic, and psychological approaches to complete the primary knowledge of neuropsychiatric disorders in general and bipolar disorder in particular.

Could the stress axis dysfunction be a fundamental dysfunction of bipolar disorder, or on the other hand, it is a tributary effect? While both directions of causality are possible, there are several indications that the influence of the HPA axis in the neurobiology of bipolar may play the underlying dysfunction in the vulnerability and development of bipolarity.

The primary system of the stress is HPA axis, during stressful life events (e.g., acute and chronic stress) may predispose and precipitate bipolar disorder. Intriguingly, several different early life stresses could develop permanent dysfunctions that look like some of the findings in the neurobiology of bipolar disorder. The relationship between bipolar, stressful events and the HPA axis are connected to and the impairment of the HPA axis feedback, observed in patients with bipolar disorders. This relationship could also develop in healthy first-degree relative with an affective disease. Therefore, we can conclude the importance of epigenetic and vulnerability to impair the HPA axis chronically.

The HPA axis is an essential bodily system to be clarified in the etiology of mental illnesses. However, this needs to be seen in the context that several other influences also require attention, such as genetics, the individual's relationship with the environment, early stress, and the resilience of some individuals, which may help explain interindividual differences in many of the aspects of HPA axis changes and stress responsiveness.

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