Chapter 17

Neuroendocrine and stress pathways in bipolar disorders

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17.1 Introduction

Bipolar disorder (BD) is a highly recurrent psychiatric disorder, which is characterized by abnormal mood disturbances, ranging from severe mania to severe depressive episodes, and often accompanied by functional and cognitive deficits (Watson, Thompson, Ritchie, Nicol Ferrier, & Young, 2006). Bipolar depression is common, recurrent and chronic that affects the individual's organism as a whole, affecting mood, cognitive, neuroendocrine and other body systems, impairing personal, social, and work well-being (Juruena, Gadelrab, Cleare, & Young, 2021). The unipolar and bipolar depressive conditions are phenomenological similar. Without being aware of the existence of a previous manic/ hypomanic or mixed condition, it is difficult to make a diagnosis of BD. For this reason, bipolar subjects are often misdiagnosed as unipolar (Angst et al., 2011).

The etiological factors of unipolar and bipolar depression can be genetic and environmental. Among both factors, we can mention changes in the functioning of the hypothalamus−pituitary−adrenal (HPA) axis, as well as changes in the renin−angiotensin−aldosterone system (RAAS), the receptors of these axes and their hormones (cortisol and aldosterone) receive impact of environmental life events (Young & Juruena, 2021). Early-life stress and its subtypes induce persistent changes in the ability of the HPA axis to respond to stress in adulthood, and this fact can lead to a greater susceptibility to the development of depression and bipolar depression (Etain & Aas, 2020; Juruena, Gadelrab, et al., 2021). These axis abnormalities seem to be related to changes in the ability of circulating cortisol to exert negative feedback on the secretion of hormones from the HPA axis in individuals with depression and BD. These patients are more likely to have a hyper- or hypofunctional HPA axis (Juruena, Werne Baes, Menezes, & Graeff, 2015; Von Werne Baes, de Carvalho Tofoli, Martins, & Juruena, 2012).

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These observations correspond with the hypothesis according to which, stress-related depression may represent a separate endophenotype characterized, among other factors, by increased HPA axis function (Juruena et al., 2015). According to some authors, stress could lead to the onset of the first depressive episode in genetically vulnerable individuals, making them even more sensitive to stress in a fast forwarding fashion, compatible with the kindling hypothesis by (Post, 1992), with this, the individual would need less stress to trigger new crises, and it would become more vulnerable to the reprint of new depressive episodes before different, sometimes milder, stressors (Post, 1992). Thus as the HPA axis is activated in response to stressors, changes in the functioning of this axis, at any level of its components, and its regulations may play a pivotal etiological role in the onset of BDs (Post, 2021).

17.2 The hypothalamus–pituitary–adrenal axis

The HPA axis constitutes one of the major endocrine systems that maintain homeostasis when the organism is challenged or stressed. Activation of the HPA axis is perhaps the most important endocrine component of the stress response. While short-term stress does not lead to longitudinal negative, chronic stress can result in negative health outcomes (Sapolsky, Romero, & Munck, 2000).

The functioning of the HPA axis is shown schematically in Fig. 17.1. This axis acts on the release of cortisol when the suprachiasmatic hypothalamic neurons release the corticotrophin-releasing hormone (CRH) and vasopressin (AVP), which in turn, stimulate the release of adrenocorticotropic hormone (ACTH), which will promote the release of cortisol by stimulating the adrenal cortex. The released cortisol will bind to the receptors, resulting in diverse responses, including negative feedback, enclosing the hormonal cortisol release loop. ACTH increases the production of steroid hormones, including aldosterone, by mobilizing cholesterol in the adrenal cortical cells. After the release of cortisol, it will perform a negative feedback response to cease its release (Juruena, Cleare, & Young, 2021; Young & Juruena, 2021).

Abnormal activation of the HPA axis, with increased circulating levels of cortisol, is one potential explanation for many of the features of depression, and many previous studies have described an impaired HPA negative feedback, leading to hypercortisolemia, in the more severe forms of depression and mania (Gold, Goodwin, & Chrousos, 1988; Nemeroff & Evans, 1984).

Cortisol mediates its action, including feedback regulation of the HPA axis, through two distinct intracellular corticosteroid receptor subtypes referred to as mineralocorticoid receptors (MRs) and glucocorticoid receptors (GRs) (de Kloet, Vreugdenhil, Oitzl, & Joels, 1998; McEwen, 2000). The type I receptor (MR) has a limited distribution and is found in relatively high density in the hippocampus (Reul, van den Bosch, & de Kloet, 1987) and in sensory and motor sites outside the hypothalamus (Arriza, Simerly,

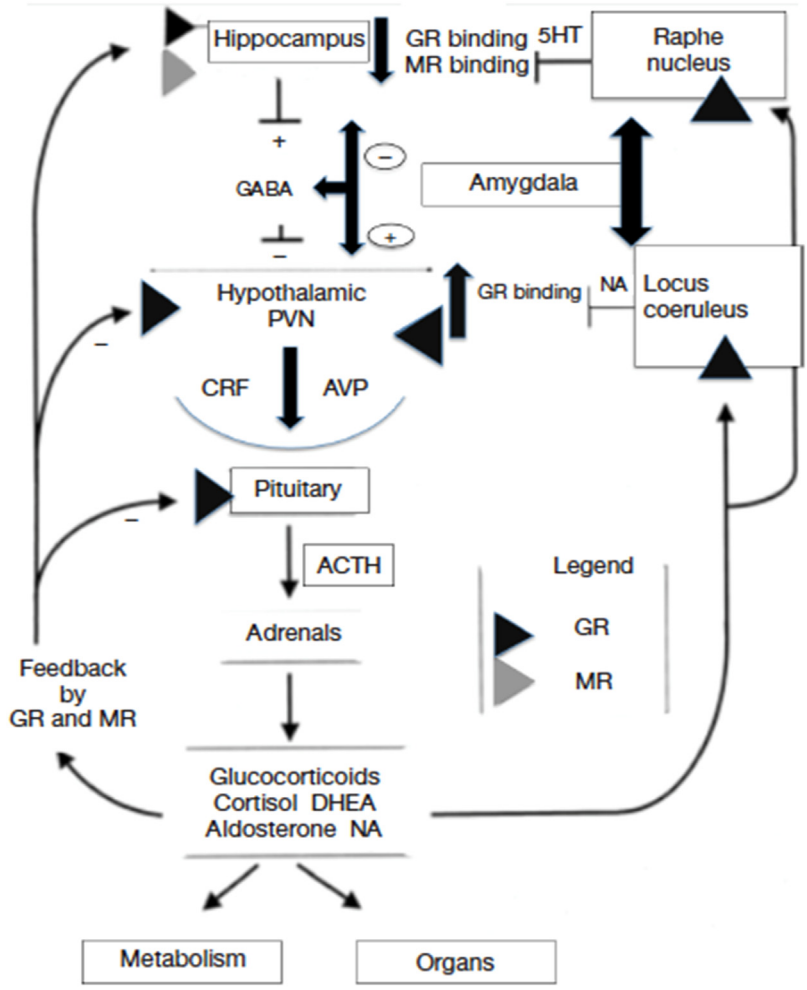

FIGURE 17.1 Simplified diagram showing the functioning of the hypothalamus−pituitary-adrenal (HPA) axis negative (−) feedback. *ACTH*, Adrenocorticotrophic hormone; *AVP*, vasopressin; *CRH*, corticotrophic hormone (corticotrophin); +, stimulus for release; −, inhibition of release. It shows HPA axis regulation and (−) feedback of cortisol via glucocorticoid receptors (GRs) and mineralocorticoid receptors (MRs). Including hippocampus, amygdala, raphe nucleus, locus coeruleus and relation via serotonin (5HT) and noradrenaline (NA) with GR/MRs and adrenal hormones. *Adapted from Juruena, MF, Gadelrab, R, Cleare, AJ, & Young, AH (2021). Epigenetics: A missing link between early life stress and depression. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 109, 110231.*

Swanson, & Evans, 1988). The expression of type II receptors (GR) is more widespread and is found in the hippocampus, amygdala, the hypothalamus, and the catecholaminergic cell bodies of the brainstem (Fuxe, Harfstrand, & Agnati, 1985), see Fig. 17.1.

There is a theory that suggests a GR defect may mediate the impaired negative feedback thought to cause hypercortisolemia in some bipolar patients (Watson, Gallagher, Ritchie, Ferrier, & Young, 2004). Under basal levels of cortisol, negative feedback is mediated mainly through the MR in the hippocampus, whereas under stress and high cortisol concentrations, feedback is mediated by the less sensitive GR in the hippocampus, hypothalamus, and pituitary (de Kloet et al., 1998). The balance in these MR- and GR-mediated effects on the stress system is of crucial importance to the set point of the HPA axis activity (de Kloet et al., 1998). It is proposed that the maintenance of corticosteroid homeostasis and the balance in MR/GR-mediated effects limit vulnerability to stress-related diseases in genetically predisposed individuals (Juruena, Agustini, Cleare, & Young, 2017).

17.3 Steroid hormones

Steroid hormones (mineralocorticoids, glucocorticoids, and steroids) are produced from cholesterol. Cortisol is the hormone responsible for 95% of glucocorticoid activity and aldosterone is responsible for 90% of mineralocorticoid activity. Both cortisol and aldosterone are produced in the adrenal cortex—cortisol in the fasciculated region, and mineralocorticoids in the glomerulosa (de Kloet & Joëls, 2017). In humans, the concentration of circulating glucocorticoids is higher than the concentration of circulating aldosterone. Cortisol and aldosterone can be transported linked to proteins—such as transcortine (cortisol) and albumin—or in their free form. Both hormonal forms, linked to proteins or free, are transported through the extracellular fluid compartment. As cortisol has most of its fraction—90%−95%—linked to carrier proteins, its half-life is longer—60−90 minutes. Aldosterone has a shorter half-life—about 20 minutes—as only 60% is linked to the protein, accelerating its elimination. The metabolization of glucocorticoids and mineralocorticoids is done in the liver, where they are degraded and conjugated especially with glucuronic acid and, a small part, with sulfates. A quarter of such conjugates are eliminated in the feces and bile, whereas the rest are freely loaded into the plasma and through renal filtration, will be eliminated through the urine. The action of cortisol and aldosterone occurs from its binding to receptors called MR and GR (de Kloet & Joëls, 2017; Gomez-Sanchez & Gomez-Sanchez, 2014).

17.4 Mineralocorticoid receptors and glucocorticoid receptors

In 1988, Arriza and collaborators (Arriza et al., 1988), after cloning human GR and MR, demonstrated the differences in responsiveness of GR and MR to cortisol. MRs would be responsible for responses to glucocorticoids at baseline level, whereas GRs would be more responsible when there was a

high level of circulating cortisol, such as those that occur in situations of stress, circadian peaks/waves, in response to inflammation, or gluconeogenesis in a situation hypoglycemia (Arriza et al., 1987; de Kloet, Joëls, & Holsboer, 2005).

The mineralocorticoid activity of aldosterone is high enough to maintain activation of the activated receptor at hourly intervals. GR, on the other hand, responds in an ultradian rhythms, considering its low affinity for cortisol and which is activated progressively by increasing the frequency and amplitude of hormonal cortisol releases, such as those that occur in situations of great or continuous stress and in the circadian peaks (de Kloet et al., 2005). The GR in the cytoplasm are monomers that interact directly with other extranuclear regulatory proteins and alter gene expression indirectly. When inactive, the GR in the cytoplasm is linked to inactivating proteins, such as chaperones (e.g., hsp90, hsp70, hsp56). The GR in the cytoplasm can have nongenomic actions, where they produce rapid changes in the activity of signal transduction pathways (Lösel et al., 2003; Pratt, 1993), see Fig. 17.2 (Juruena, 2014).

Although MR has an affinity for cortisol greater than GR (10 times greater), it gets its name because it plays a key role in hemodynamic homeostasis by modulating the transport of ions and fluids when bonding with mineralocorticoids (Gomez-Sanchez & Gomez-Sanchez, 2014; Murck, Büttner, Kircher, & Konrad, 2014). In the older literature, considering its high affinity, MR was known as a type 1 corticosteroid receptor, whereas GR was known as a type 2 corticosteroid receptor (Lembke et al., 2013; Murck, Ploch, & Montgomery, 2018). The receptors can act synergistically or antagonistically. MRs would act in a limited part of the gene network responsive to GR, when cortisol levels are low. However, maximum gene activity would occur when there was GR activity, which is stimulated by higher levels of cortisol, such as when in stressful situations (De Kloet & Joëls, 2017; Meijer, Steenbergen, & de Kloet, 2000; Reul & de Kloet, 1985).

Initially, cortisol binds to slow-acting MRs, due to its greater affinity and continuously, even when the hormone is present at baseline levels. Such receptors are continuously activated and regulate the stress response threshold. Slow-acting MRs promote the traffic of ion channels and receptors between the intracellular compartment and the cell surface. If cortisol levels increase in the face of an acute stress situation, rapid response (nongenomic) MRs are activated in a matter of minutes. Such MRs are located on or near the plasma membrane of presynaptic and postsynaptic terminals—mainly presynaptic ones—and have a lower affinity for cortisol than the slow-acting MR. The fast-acting MRs will act on voltage-gated or ligand-dependent ion channels, increasing the probability of the release of glutamate synaptic vesicles. At this time, there is also lateral motility of the subunits of glutamate receptors (de Kloet et al., 2005; Gomez-Sanchez & Gomez-Sanchez, 2014; Joëls, Karst, Derijk, & de Kloet, 2008), see Table 17.1.

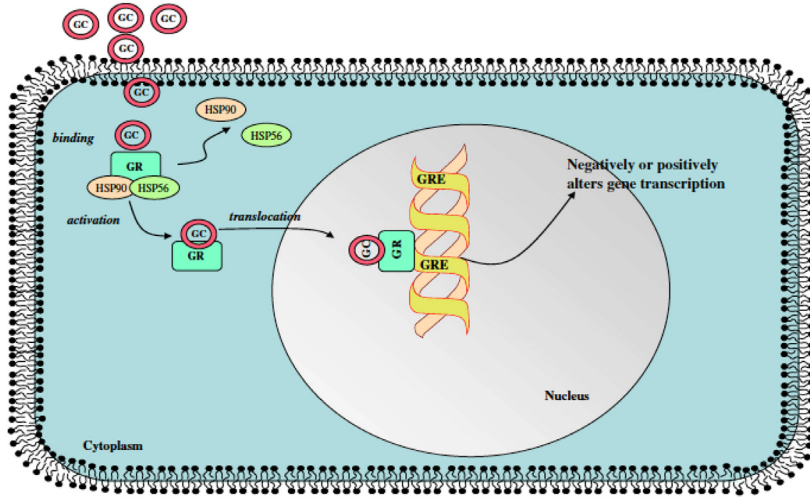

FIGURE 17.2 Diagram of the epigenetic properties of cortisol and the glucocorticoid receptor (GR) stimulation, this receptor exists in almost every tissue of the human body, at the cytoplasm with chaperonin proteins with numerous proteins (HSP56, HSP90). After cortisol the glucocorticoid (GC) binds as 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. GC also appears to exert its effects directly in the cell mitochondria. *Adapted from Juruena, MF, Gadelrab, R, Cleare, AJ, & Young, AH (2021). Epigenetics: A missing link between early life stress and depression. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 109, 110231; Juruena MF (2014). Early-life stress and HPA axis trigger recurrent adulthood depression. Epilepsy & Behavior, 38, 148–159.*

TABLE 17.1 Two intracellular corticosteroid receptor types in the brain.

Mineralocorticoid receptor	Glucocorticoid receptor
High affinity for corticosteroid	Lower affinity for corticosteroid
In limbic brain structures	Ubiquitous
Agonist: aldosterone	Agonist: dexamethasone, RU 28362
Antagonist: RU 26752, spironolactone	Antagonist: RU 38486

Source: Adapted from Juruena, M. F., Werne Baes, C. V., Menezes, I. C., & Graeff, F. G. (2015). Early life stress in depressive patients: Role of glucocorticoid and mineralocorticoid receptors and of hypothalamic-pituitary-adrenal axis activity. *Current Pharmaceutical Design, 21*(11), 1369–1378.

Considering the cognitive context of the action of fast and slow action MR, the fast action would act in the learning of a simple strategy to facilitate the codification of aversive memory. The slow-acting MR, on the other hand, would improve the formation of conceptual memories, as well as

improve working memory and the ability to make decisions more rationally, with less emotional interference. The delayed response of this MR in relation to the membrane is important for poststress recovery and storage of information that is relevant for future use. Membrane MRs act synergistically with the CRH receptor, AVP and melanocortins for neuroendocrine, sympathetic, fear, or fight-or-flight reactions. In the meantime, GRs are trying to smooth out the initial stress reactions. The proper balance of the functioning of MR / GR is essential for the homeostasis of the organism, or its lack can result in inadequate or excessive functioning, compromising resilience and promoting the phenotype vulnerable to diseases related to exposure to stress (de Kloet et al., 2005; Joëls et al., 2008; Joëls, Pasricha, & Karst, 2013) (Table 17.2).

Reul and de Kloet (Reul et al., 2015) described the distribution of MR and GR in the rat brain and their affinity for corticosteroid binding. It was possible to observe the considerable topographic difference in the brain as a whole and in the hippocampus between the two receptors. MR would be more restricted to the lateral septum and hippocampus (dorsal subiculum, CA1, and dentate gyrus). GR would be more dispersed across the regions of the lateral septum, dentate gyrus, solitary tract nucleus, cortical amygdala, paraventricular nucleus (PVN), locus coeruleus (LC), hippocampal subiculum, and CA1 region. The GR distribution is varied and unequal by

TABLE 17.2 Function of brain corticosteroid receptors.

Corticosterone condition	Occupied receptor	Function
Basal	MR	Stabilization of excitability
		Sensitivity Stress Response System
		Proactive feedback
		Selection of behavioral response
Stress	MR + GR	Suppression increased excitability
		Recovery from stress-induced activation
		Reactive feedback
		Facilitation of memory storage

Abbreviations: *MR*, mineralocorticoid receptor; *GR*, glucocorticoid receptor.
Source: Adapted from Juruena, M. F. (2014). Early-life stress and HPA axis trigger recurrent adulthood depression. *Epilepsy & Behavior, 38*, 148–159; Joëls, M., Karst, H., Derijk, R., & de Kloet, E. R. (2008). The coming out of the brain mineralocorticoid receptor. *Trends in Neurosciences, 31*(1), 1–7; Joëls, M., Pasricha, N., & Karst, H. (2013). The interplay between rapid and slow corticosteroid actions in brain. *European Journal of Pharmacology, 719*(1–3), 44–52.

neurons and glial cells and its greatest density would be in the hypothalamic PVN region and in the afferent limbic neurons that modulate transsynaptically PVN by ways that reinforce with a hypothalamic inhibitory network. Glutamate release in the **PVN** is tonically inhibited by **GABA** A receptor activation (de Kloet et al., 2005; Reul et al., 2015). High concentrations of GR are also present in the hippocampus, neocortex, and supraoptic nucleus. The limbic system expresses MR mainly in the dentate gyrus, hippocampal CA1 and CA2 areas, lateral septum, and amygdala. The coexpression of MR and GR can be clearly seen in pyramidal cells of the hippocampus, dentate gyrus, tonsillar nucleus, and septal lateral and cortical areas (Joëls et al., 2013; Meijer et al., 2000; Reul et al., 2015).

The interaction of the RAAS and the HPA axis has been increasingly emphasized. Murck et al. (2014) and Murck, Schüssler, and Steiger (2012) clearly demonstrated the importance RAAS, the forgotten stress hormone system, and the interaction between RAAS and other important systems. Sympathetic activity and secretion of neuropeptides CRH and AVP by the hypothalamus PVN stimulates the pituitary to release ACTH. ACTH will induce the adrenal cortex to secrete cortisol. The RAAS, moreover, the sympathetic activity depends on the activation of the LC, which is connected to the PVN, making this cycle have a positive feedback. After noradrenaline (NA) is produced by the sympathetic nervous system, NA increases the secretion of CRH (from the PVN) and this, in turn, activates the release of NA by the LC. The sympathetic nervous system will send a signal to convert angiotensinogen to angiotensin I (ATI) by the enzyme renin, and ATI will be converted to angiotensin II (ATII) by the angiotensin-converting enzyme (ACE). ATII will stimulate the release of aldosterone from the adrenal cortex (Murck et al., 2012, 2014).

17.5 Neuroendocrine function test

To assess the functioning of GR and MR in subjects with depression, some researchers, from the 70, started to perform pharmacological challenges. Such challenges consist in the administration of GR and MR agonist and antagonist drugs and the observation of cortisol levels (Juruena et al., 2015; Von Werne Baes et al., 2012; Watson et al., 2004). The dexamethasone suppression test (DST) was the first, and is to date the most studied, biological marker in research on affective disorders. In 1968 Bernard Carroll and colleagues showed (Carroll, Martin, & Davies, 1968) that depressed patients fail to suppress plasma cortisol to the same extent as nondepressed control subjects (Carroll et al., 1968). Early studies in the 1980s proposed the use of the DST to diagnose the melancholic subtype of depression and pointed to the high specificity of the DST in melancholia (Carroll, Feinberg, & Greden, 1981). However, in the 1990s, several studies found that the sensitivity of the DST in the diagnosis of the DSM-III defined melancholic subclass of

major depression was only approximately 35%–45%, although the specificity was higher at approximately 70%–89% (Rush, Giles, & Schlesser, 1996). A metaanalysis to determine the significance of differences in rates of nonsuppression of cortisol indicated a high probability that a greater rate of cortisol nonsuppression occurs in psychotic depression (64% vs 41% in nonpsychotic patients), probably including bipolar patients (Nelson & Davis, 1997; Ribeiro, Tandon, Grunhaus, & Greden, 1993). In summary, studies using the DST have shown that a high proportion of patients with various affective disorders have elevated cortisol levels that escape the suppressive effect of dexamethasone. The use of dexamethasone for a suppressive test has the advantages that it does not crossreact in most cortisol radioimmunoassay (RIA) and is not subject to reactivation by 11-beta-hydroxysteroid dehydrogenase type 1 in central feedback sites (Arana, Baldessarini, & Ornsteen, 1985). Unfortunately, dexamethasone has pharmacodynamic and pharmacokinetic features that are very distinct from those of the human endogenous glucocorticoid, cortisol. For example, dexamethasone does not bind to the corticosteroid-binding globulin (CBG) and has a longer half-life than cortisol (Juruena et al., 2006; Pariante, Papadopoulos, & Poon, 2002). Furthermore—and the most important of these distinctive features—dexamethasone and cortisol differ in their abilities to bind and activate the GR and the MR, dexamethasone can fully activate human GR-mediated gene transcription, but even at the highest concentrations is unable to fully activate human MR-mediated gene transcription (Rupprecht et al., 1993), possibly because the dexamethasone–MR complex is much less stable than the dexamethasone–GR complex (Reul et al., 2000). Therefore the DST can only investigate the GR in bipolar patients.

The most sensitive neuroendocrine function test to detect HPA dysregulation, until now, combines the DST and the CRH stimulation test in the dexamethasone suppression/CRH stimulation (DEX/CRH) test (Heuser, Yassouridis, & Holsboer, 1994; von Bardeleben & Holsboer, 1991). Indeed, Heuser et al. (1994) concluded from their studies that the sensitivity of this test is above 80%, depending on age and gender. Watson et al. (Watson, Gallagher, Smith, Ferrier, & Young, 2006) compared the use of the DEX/CRH test and the DST in bipolar patients with mood disorders and control subjects. They found a close correlation between the cortisol responses on the two tests. The sensitivity of DEX/CRH was 61.9% and the specificity 71.4%, whereas the sensitivity of the DST was 66.6% and the specificity was 47.6%. This suggests that the two tests measure common pathology, but that the DEX/CRH test is more specific and hence has better diagnostic utility (Watson, Gallagher, et al., 2006).

Nevertheless, the DEX/CRH test remains limited by the pharmacokinetic profile of dexamethasone and the lack of MR receptor activity and is not practical. Therefore until recently, there were no tests that could fully assess

the contribution of both GR- and MR-medicated negative feedback in the HPA axis overactivity of depression.

However, we have developed the prednisolone suppression test (PST) (Juruena et al., 2006, 2009; Pariante et al., 2002). Prednisolone is a synthetic glucocorticoid, such as dexamethasone, is widely used as an antiinflammatory and immunosuppressive drug. Prednisolone mimics cortisol in many ways. Like cortisol, it binds to CBG, and its half-life is similar to that of cortisol. However, the most important of these similarities is that prednisolone and cortisol are similar in their abilities to bind and activate the GR and the MR (Juruena et al., 2006; Pariante et al., 2002).

In studies examining human GR, prednisolone has an affinity that is twofold higher than that of cortisol, whereas dexamethasone has an affinity than is sevenfold higher than that of cortisol (Ballard, Carter, Graham, & Baxter, 1975); and in another study examining mouse GR, prednisolone has a relative potency to activate GR function that is the same as cortisol, whereas dexamethasone has a relative potency that is fourfold higher than that of cortisol (Ballard et al., 1975), see Table 17.1.

Therefore prednisolone is similar to cortisol in its ability to probe both the GR and the MR. Of course, an important advantage of using prednisolone, rather than cortisol, as a test for both the GR and the MR, is that this avoids the confounding effects of the persistence in circulation of the administered cortisol. Indeed, prednisolone is particularly useful in examining suppression of salivary cortisol (Juruena et al., 2006; Pariante et al., 2002), which represents the bioavailable fraction (5%−10%) of plasma cortisol, and therefore reflects more accurately the hormone that reaches and binds the corticosteroid receptors (Reul & de Kloet, 1985) (Table 17.3).

The evidence summarized above suggests that prednisolone is similar to cortisol in its ability to probe both the GR and the MR, and theoretically provides a more naturalistic probe than dexamethasone. Indeed, prednisolone is particularly useful in examining the suppression of salivary cortisol,

TABLE 17.3 Characteristics of dexamethasone/prednisolone suppression tests.

	Dexamethasone	Prednisolone
Pharmacodynamic	GR	MR /GR
Pharmacokinetic	Long 1/2 life	≅Cortisol
CBG binding	Does not bind	Bind

Abbreviations: *CBG*, corticosteroid-binding globulin; *GR*, glucocorticoid receptor; *MR*, mineralocorticoid receptor.
Source: Adapted from Juruena, M. F., Cleare, A. J., Papadopoulos, A. S., Poon, L., Lightman, S., & Pariante C. M. (2006). Different responses to dexamethasone and prednisolone in the same depressed patients. Psychopharmacology, 189(2), 225−235.

which represents the bioavailable fraction (5%−10%) of plasma cortisol, and therefore more accurately reflects the hormone that reaches and binds the corticosteroid receptors (Kirschbaum & Hellhammer, 1994). In contrast, salivary cortisol responses to dexamethasone show a large variability (Juruena et al., 2010). We used an MR agonist (prednisolone) to test directly the ability of the MR to suppress the HPA axis, rather than inferring this ability by blocking MR with an antagonist, and it is striking that these two different approaches reach the same conclusion. It is intriguing to speculate that the (hyper)functional MR could represent a protective mechanism that prevents further biological and clinical deterioration in depressed and bipolar patients.

In summary, as endogenous HPA axis feedback involves both GR and MR and given the above suggestions that in depression and bipolar MR can compensate for altered GR function, we believe that prednisolone provides a more valid test of the HPA axis in depression, and one distinct from dexamethasone (Juruena et al., 2006, 2010; Reynolds et al., 1998).

A number of prior studies have also investigated whether HPA axis dysfunction is associated with subsequent response to treatment. Our study described above also went on to look at the subsequent response to intensive, inpatient treatment in this group of patients in order to assess whether the PST on admission was a predictor of their subsequent response to treatment (Juruena et al., 2009). A particularly interesting aspect of these findings was that, although this group of patients with depression as a whole showed preserved negative feedback, this did not apply to all patients. Thus after intensive treatment, just over half the participants (53%) were classified as treatment responders, with a concomitant improvement in several clinical measures. Those classed as nonresponders had been prospectively treated with an intensive, evidence-based treatment package and thus represent a well-defined and truly treatment-resistant population. The PST was able to distinguish these two groups prospectively; thus there was a higher postprednisolone cortisol release (representing impaired suppression) in the severely treatment-resistant group compared with the treatment-responsive group. In contrast, no relationship was found with clinical response for basal cortisol levels. Thus all patients showed HPA axis overactivity, whereas the severely treatment resistant group also showed nonsuppression after prednisolone and hence an abnormally impaired negative feedback system (Juruena et al., 2009).

The implication of this is that there may be a subgroup of patients within those who are severely ill who have significant neuroendocrine dysfunction, represented by a disturbed HPA axis feedback and an imbalance in the ratio of MR /GR signaling, who are less responsive to the treatments that are currently available. It may be that the underlying difference in these patients is an inability to compensate for GR resistance by increased MR function (Juruena et al., 2009, 2013).

17.6 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, whereas new recurrences may become autonomous and independent of environmental triggers (Post, 2007, 2010).

Specifically, the progression of BDs 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 BD 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 17.4.

The HPA axis dysfunctions in also occurs during bipolar depressive, manic, hypomanic, and mixed episodes. Studies with DEX showed an alteration in cortisol in manic episodes in mixed characteristics (Evans & Nemeroff, 1983; Swann et al., 1992). A study that used the DEX/CRH test in bipolar with manic episode had increased suppression to the DEX/CRH test when compared to healthy controls; these alterations could be observed

TABLE 17.4 Psychoneuroendocrine 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

Source: Adapted from Juruena, M. F., Cleare, A. J., & Young, A. H. (2021). Neuroendocrine stress system in bipolar disorder. *Current Topics in Behavioral Neurosciences*, 2021;48:149-171; McEwen, B. S. (2000). Allostasis and allostatic load: Implications for neuropsycho-pharmacology. *Neuropsychopharmacology*, *22*(2), 108–124; Young, A. H., & Juruena, M. F. (2021). The neurobiology of bipolar disorder. *Current Topics in Behavioral Neurosciences*, 2021;48:1–20.

after treatment in response and/or remission in bipolar patients in the manic phase (Schmider et al., 1995). A study described cortisol was significantly increased at night in manic patients compared to healthy controls (Linkowski et al., 1994). Bipolar in mania and/or hypomania, depression and/or euthymia, increase cortisol levels when compared to healthy subjects (Cervantes, Gelber, Kin, Nair, & Schwartz, 2001). The impair in the (−) feedback at central neuroendocrine system in controlling corticosteroids can develop amplified rise in these hormones during stressful events and declines the HPA axis' capacity to restart to baseline concentrations (Tatro, Everall, Kaul, & Achim, 2009). The augmented levels may have longstanding effects in bipolar patients, since corticoids perform vital functions as allostatic moderators with neurotransmitter systems and brain peptides (McEwen, 2004). Furthermore, changing neuroplasticity, HPA axis can influence the circadian rhythm, for example, cycle vigil/sleep (Murray & Harvey, 2010). Higher cortisol levels have also been showed as a vulnerability biomarker in family members of patients with BDs (Ellenbogen, Hodgins, Linnen, & Ostiguy, 2011).

In BD, there are some controversy data relate to HPA axis activity. One study described that first episode drug-naïve mania demonstrated lower cortisol released compared to healthy subject, with positive correlation with irritability and elevated mood correlated with lower levels of cortisol (Valiengo et al., 2012). Another study compared bipolar and borderline personality disorder assessing the impact associated with early-life stress, and cortisol, the authors found that borderline personality patients had a more severe history of early-life stress than bipolar overall and in patients with history of emotional neglect, physical neglect, and emotional abuse than bipolar patients. The history of early-life stress in patients with borderline personality disorder and BD 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, Cleare, Young, & Juruena, 2019).

17.7 Conclusion

The evidence described in this review provide support defining the impact of the HPA axis in the physiopathology of bipolar disorders (BD); however, it is crucial to highlight that BD is a very multifaceted and comorbid clinical syndrome, as the current state of the evidence is insufficient to allow its characterization based on neurobiology.

To understand better the relationship between vulnerability and stressful environment in the genesis of BD 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 BD in particular.

Furthermore, it is possible that there is a dissociation between GR and MR function present in subgroups of patients of the bipolar spectrum, which has not yet been determined using existing tools. We suggest that future studies might usefully examine the HPA axis in larger samples of bipolar patients (including different subtypes of the bipolar spectrum) and in nonpsychiatric populations of individuals with early- and adult-life stressors. In addition to providing potential insights into the mechanism of treatment resistance, this finding, if replicated, could have clinical utility and deserves further study.

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