Early Life Stress in Depressive Patients: Role of Glucocorticoid and Mineralocorticoid Receptors and of Hypothalamic-Pituitary-Adrenal Axis Activity

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Abstract: Depression is a chronic, recurrent and long-term disorder characterized by high rates of impairment and several comorbidities. Early life stress (ELS) is associated with the increased risk for developing depression in adulthood, influencing its clinical course and predicts a poorer treatment outcome. Stressful life events play an important role in the pathogenesis of depression, being well established as acute triggers of psychiatric illness. The vulnerability for developing depression is associated to changes in neurobiological systems related to stress regulation. The hypothalamic-pituitary-adrenal (HPA) axis responds to external and internal stimuli. Reported results indicate that stress in early phases of development can induce persistent changes in the response of the HPA axis to stress in adulthood, leading to a raised susceptibility to depression. These abnormalities appear to be related to the HPA axis deregulation in depression, partially due to an imbalance between glucocorticoid receptors (GR) and mineralocorticoïd receptors (MR). While most studies have consistently demonstrated that GR function is impaired in major depression (reduced GR-mediated feedback in HPA axis), data about the MR role in depression are still limited and controversial. Thus, in this review article we summarize the main reported findings about the consequences of ELS in HPA axis functioning and in the responsivity of MR/GR receptors in depression.

Keywords: Early life stress, Depression, Glucocorticoid receptor, Mineralocorticoid receptor, Hypothalamic-Pituitary-Adrenal axis.

INTRODUCTION

Depression is a chronic, recurrent and long-term disorder characterized by high rate of disabilities, as well as personal and financial losses. Currently available treatments of depression present limited efficiency. Although many scientific studies are being developed to better understand the factors involved in the etiology of depression, there still are many gaps that need to be investigated, mainly regarding on what traumatic events during childhood influence the development of depressive disorders in adulthood.

Furthermore, considering that stress usually activates the hypothalamic-pituitary-adrenal (HPA) axis, it is fundamental to comprehend the impact of early life stress (ELS) in the functioning of HPA axis and in the responsivity of regulatory mineralocorticoid receptors (MR) and glucocorticoid receptors (GR) in depressive illness, for developing new diagnostic tools and therapeutic strategies.

EARLY LIFE STRESS

The concept of ELS encompasses a wide range of traumatic experiences during early childhood to adolescence, such as parental loss, divorce of parents, caregivers with psychiatric disorders, family violence, infant disease, absence of basic care, neglect, deprivation of adequate food and shelter and lack of moral support and encouragement [1-3].

Childhood maltreatment is a major social problem. It is a complex global phenomenon that can result in serious physical injury, and even death. Moreover, its psychological consequences can severely affect the child's mental health well into adulthood [4-5]. ELS is associated with a diverse range of psychiatric disorders, rendering some individuals vulnerable to certain types of psychopathology, especially depression, posttraumatic stress disorder (PTSD), and substance abuse [11, 12, 13]. Many epidemiological studies have documented significant associations between ELS and psychiatric disorders, such as mood and anxiety disorders, in adulthood [14-17]. These studies demonstrate that ELS may adversely affect the child's development, triggering severe and disabling psychiatric disorders in adult life [18, 20]. Approximately, one-quarter to one-third of abused children meet the criteria for major depression when they reach the end of second decade of life [21].

DEPRESSION

Major depressive disorder (MDD) is a chronic disease, with high recurrence rate, which is frequently associated with functional

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disability and impairment of physical health [22-24]. Depressive subjects have impaired daily activities and reduced feelings of well-being feeling; they also require of health services more frequently [25, 26]. The suicide rate among these patients ranges from 15 to 20% [27]. Despite its higher incidence in middle-aged population, this disorder may affect people at any age [28]. Depression in adulthood is related to a higher risk for developing cardiovascular disease, diabetes, metabolic disorders, and dementia [29, 30].

During the five-year period after the treatment of the first depressive episode, about 60% of patients will present a second depressive episode, and, in average, four depressive episodes during their lifetime [31]. Non-remitting depression was characterized by three main factors: anxiety, cognitive difficulties and sleep disturbance [32]. Also, with antidepressant medication, 30 to 50% of depressive subjects do not remit their depressive symptomatology [33]. Because of the high prevalence, recurrence rate of this disorder, and the limited efficacy of drug treatment, many researchers are trying to better understand the etiology and physiopathology of depression, as well as looking for biological and psychosocial factors that predict treatment outcome.

The etiological factors for depression development arise from genetic and environmental sources. Although genetic determinants are important for depression development, reported data also show that environmental factors are relevant triggers of depressive episodes [34]. Some studies demonstrate that about 60% of depressive episodes are preceded by exposure to adverse life events. Therefore, stressful conditions play an important role in the pathogenesis of depressive disorders, and are well-established acute triggers of psychiatric illness in genetically predisposed individuals [34-36]. In regard to early stressors, the studies reviewed by Raabe & Spengler [37], indicate that exposure to ELS adversity in childhood gives rise to a vulnerable phenotype, which predisposes to disease upon a new exposure to trauma and stress during lifetime, in special to depression. However, not every individual exposed to ELS adversity will inevitably develop disease upon a new exposure to trauma and stress; also, not all adults with depression have experienced ELS.

Conditions of ELS, such child abuse, neglect or parental loss have been associated with significantly increased risk for developing depression in adulthood [11, 12, 38, 39], tripping depression development in adulthood [40] and doubling depression recurrence [41]. Similar data were reported in a recent systematic review conducted by Martins et al. [39], revealing that the severity of ELS and its subtypes correlate with the severity of depression. Gibbs et al. [18] have also specifically shown that emotional abuse increases depression symptoms in adulthood. Other studies suggest that an increase of suicidal ideation in adulthood occurs in depressed patients with ELS [14, 42, 43]. Some studies further indicate that ELS aggravates the clinical course of depression and predicts poorer treatment outcome [44, 45].

**HYPOTHALAMIC-PITUITARY-ADRENAL AXI**

The HPA axis plays a fundamental role in the organism’s response to external and internal stimuli, including psychological stressors [46]. Also, it is potentially involved in the physiopathology of psychiatric disorders, particularly, in major depressive disorder (MDD) and in the mechanism of action of psychotherapeutic drugs. Depressive patients present impaired HPA axis balance, evidenced by altered concentrations of cortisol in blood and saliva. It is noteworthy the significant percentage of patients with MDD that exhibit increased concentrations of cortisol, exacerbated response to ACTH, and enlarged pituitary and adrenal glands [47-49].

However, it is necessary to emphasize that depression is a heterogeneous disorder that involves a wide range of subtypes (for example, melancholic, atypical, psychotic), with distinct characteristics in terms of symptomatology, neurobiology, and physiological and endocrine functioning [48, 50-52]. Thus, besides different clinical features and response to treatment, melancholic and atypical depressive states seem also to differ in underlying pathophysiological mechanisms, and some authors have called attention to the important role of the HPA axis in the etiology of the distinct subtypes of depression [48-52].

The most consistent findings in the literature show increased activity of the HPA axis in melancholic depression evidenced by hypercortisolemia and reduced inhibitory feedback [47-53]. Chrousos & Gold (50) suggest that melancholic depression would be characterized by excessive activation of both systems of physiological stress - locus coeruleus-noradrenergic system and HPA axis, resulting in noradrenergic and HPA axis hyperactivity, with increased cortisol production.

On the other hand, atypical depression has been associated to hypoactivity of the HPA axis, lower activity of corticotropin releasing hormone (CRH), hypocortisolism, and decreased activity of afferent noradrenergic pathways [48-52, 56-59]. The diminished activity of CRH could be specifically linked to the hypoactivation symptoms (hypersonia, hyperfagia, lethargy, fatigue and relative apathy) that are present in atypical depression [50].

Also, there are distinct degrees of efficacy for different treatments according to the subtype of depression. Besides clinical classification of depressive disorder subtypes, Parker et al. [61] suggest a functional and structural model which associates different neurotransmitter alterations to different depression subtypes. According to this model, atypical depression would be associated mainly to serotonin neurotransmission. On the other hand, in melancholic depression there would be, in addition to serotonin dysfunction, participation of norepinephrine alterations, which would be preponderant in this depression subtype [61, 62]. According to these authors, the clinical identification of MDD subtype could guide the choice of a more suitable antidepressant for each patient, taking into account the neurotransmission system involved in each case [62]. As well, several studies have associated melancholic depression to biological determinants and the atypical subtype to psychosocial determinants [63].

It is important to highlight that bipolar depression is often erroneously diagnosed in clinics as atypical unipolar depression. These patients present more frequent suicidal ideation than patients with unipolar depression [32, 64]. Considering the activity of HPA axis in patients with BD, Valiengo et al. [65] observed that when they were in the manic phase, they presented low cortisol levels in plasma, like subjects with atypical unipolar depression, compared to controls. However, in the same study, when patients with BD presented marked symptoms of irritability, they had higher cortisol levels, like the subjects with melancholic unipolar depression, compared to controls. Corroborating these data, Maripuu et al. [66] found low serum levels of cortisol in 70% of patients with BD, associated to a higher frequency of depression, worst quality of life, and impairment in global functioning.

Thus, in addition to the clinical characteristics and the distinct responses to treatment, several evidences show differences in the activity of the HPA axis. The key problem in diagnosis is that present psychiatric classification systems are based only on the subjective descriptions of symptoms. Although the detailed phenomenology includes the description of multiple clinical expressions, there is no accepted biological feature that separates different subtypes of depressive disorder. It is known that different depressive disorders can show similar clinical manifestations, and that the same type of disorder can manifest different ways for each case [67]. A research approach that describes reliable neurobiological findings for a given psychopathological syndrome would be an advance compared to a non-etiological classification system. When the diagnostic criteria will be able to include etiology and pathophysiology as essential elements for to a diagnostic decision-making, psychiatry will get closer to other medical specialties [67, 68].
Because HPA axis is activated in response to most stressors, ELS may also have an etiologically significant role on the axis abnormalities found in depression [69]. It has been concluded from these studies that ELS may lead to disruptions in HPA axis functioning, and that factors such as the age when the maltreatment occurred, parental responsiveness, subsequent exposure to stressors, type of ELS, and type of psychopathology or behavioral disturbance displayed, may influence the degree and pattern of HPA disturbance [69, 70].

In this sense, several reported results indicate that stress in early phases of development can induce persistent changes in the ability of HPA axis to respond to stress in the adult life, what can lead to increased susceptibility to depression [67-71]. Although there are few available studies about this issue, there seems to be a consensus on the concept that ELS is associated with alterations of the HPA axis in the early stages of life, leading to a biological vulnerability for developing depression in adulthood [71-74]. Recently, we have published a study with depressed patients divided into two groups. The first one included subjects with ELS and the second group included subjects without ELS [75]. We found a highly positive correlation between plasmatic cortisol levels and the severity of ELS (r=0.66; p=0.01), that is, the higher the severity of ELS, the higher is the plasmatic cortisol levels. In addition to this, no correlation was found between these two measures in patients without ELS (r=-0.54; p=0.20) and in controls (r=0.48; p=0.16). See Fig. 1.

Reported evidence indicates that several kinds of ELS combined with certain genetic backgrounds result in hypersensitization of some brain circuits to acute stressors. Consequently, when lasting changes in reactivity of the HPA axis happen, this results in unbalanced modulation of this axis [48, 74, 76]. Still, Chen et al. [77] observed, in animal experiments, that CRH may play a relevant role for mediating the effects of ELS. They administered CRH into the lateral ventricle of immature rats, triggering a stress response. The result was a long-term, progressive hippocampal dysfunction, cell loss, reproducing the effects of ELS [78]. However, despite strong reported evidence suggesting that ELS is associated with abnormalities in HPA axis and depression, there is no clear consensus on whether the ELS renders the HPA either hyper or hypoactive [74].

One of the mechanisms thought to be involved in these abnormalities is the impaired feedback inhibition of the HPA axis by circulating glucocorticoids [79]. In stressful situations, the human body starts a cascade of events in the HPA axis - CRH is released by the hypothalamus, triggering adrenocorticotropic hormone (ACTH) release by the pituitary, which, finally, stimulates the release of cortisol into the bloodstream by the adrenal cortex. Cortisol, to start its action, needs to bind to its intracellular receptors - two distinct subtypes: type I or mineralocorticoid receptor (MR) and type II or glucocorticoid receptor (GR) [68, 80-82]. MR and GR differ about cortisol affinity and the distribution throughout the brain. GR is distributed all over the brain, presenting lower affinity for cortisol it binds to this hormone when its seric levels are high, as in challenging or stressful situations. One of the GR functions is to balance the effects induced by stress [68, 80, 83]. MR has a higher affinity for cortisol, and occurs mainly in limbic brain structures, both cortical and subcortical. In this sense, even in basal condition, when circadian cortisol levels are low, the feedback made by cortisol is mediated mainly by MR located in the hippocampus [84]. MR act in stabilization of excitability, stress sensitivity, as a pro-active feedback and for selection of behavioral responses [68, 84-86]. Another function of MR is GR-dependent regulation [87]. Under stressful situations, hippocampal, hypothalamic and pituitary GRs start binding to cortisol [68, 84, 85] When cortisol binds to MR and GR, it acts to suppress the increased excitability, to recover from the stress-induced activation, and to start the reactive feedback and the facilitation of mnemonic formation [68]. The appropriate balance between MR and GR functioning is extremely important to a balanced HPA axis functioning [68, 84], such that in depression the cortisol feedback can be either increased or decreased, rendering the HPA axis respectively hypo- or hyper-active [79]. See Table 1.

Considering the link between impaired feedback inhibition of cortisol, unbalance of HPA axis and depression, several studies carried out along the 1970’s and 1980’s introduced some hormonal tests and challenges with GR and MR agonists and antagonists, for exploring these relationships.

GLUCOCORTICOID RECEPTOR

Most of the data about GR functioning came from dexamethasone suppression test (DST), the first challenge test to be developed, becoming a widely used research tool for the assessment of HPA function in depression during the 1980s. Carroll et al. [88] observed that severely depressed patients had non-suppression in DST. Likewise, Galard et al. [89] compared depressed patients to controls and found increased plasmatic and salivary cortisol, and increased plasmatic ACTH in depressed patients in the DST. Contreras et al. [90], also with DST test, observed higher levels of cortisol in patients with psychotic depression, and a trend of the psychotic group to have a higher rate of non-suppression compared to the non-psychotic group. They assessed the presence of psychotic

![Fig. (1). Positive correlation between plasma cortisol level and the severity of early life stress (ELS) assessed by the Childhood Trauma Questionnaire (CTQ) in depressed patients with ELS. Note: n=13; r=0.66; p=0.01. Adapted from [75].](image-url)
symptoms only in melancholic depression [90]. Although DST was widely used in initial studies, it has limited use in clinical routine and in research because of its low sensitivity (20% - 50%) [91, 92]. Also, dexamethasone’s pharmacokinetic and pharmacodynamic features are distinct from those of cortisol, since dexamethasone binds preferentially to GR, unlike cortisol that presents a higher affinity for MR [93]. About ten years after DST, [94] a more sensitive neuroendocrine functional test has been developed to detect HPA axis unbalance. This test combines DST with CRH stimulation - as a consequence it is named the DEX/CRH challenge test. It involves oral administration of a single 1.5 mg dose of dexamethasone (DEX) at 11 P.M., followed by, in the next day, at 3 P.M., an intravenous bolus of 100 μg CRH. Administration of supra-physiological doses of CRH elicits ACTH blunted response in depressives, while DEX pre-treatment produces the opposite effect and, paradoxically, enhances ACTH release following CRH. Similarly, CRH-induced cortisol release is much higher in DEX pre-treated patients than in patients treated with CRH challenge, alone. Dexamethasone, due to its low binding affinity to corticosteroid-binding-globulin (CBG) and its decreased access to the brain, acts primarily in the pituitary to suppress ACTH. The subsequent decrease of cortisol and the failure of DEX, to compensate the decreased cortisol levels in the nervous tissue, create a situation sensed by central regulatory elements of the HPA system as a partial and transient adrenalectomy. Thus, there is an increase in secretion of central neuropeptides - mainly CRH and vasopressin (AVP), which are capable of activating ACTH secretion [95]. In healthy individuals, cortisol secretion after DEX remains suppressed after the injection of CRH, unlike depressed patients, which demonstrate elevated cortisol concentrations in response to this test, probably, as a result of reduced GR sensitivity that attenuates the suppressive effects of dexamethasone at the pituitary. This failure in the inhibition of CRH and AVP secretion by the hypothalamus enhances the stimulatory effects of the exogenous CRH in Dex/CRH test [96, 97].

Several studies have used Dex/CRH challenge test to assess HPA axis to better understand the physiopathology of suicidal behavior in depressed patients. Nevertheless, these data are still controversial. Kunugi et al. [98] found a trend towards higher cortisol and ACTH levels in depressed patients that had attempted suicide, while Pfening et al. [99] observed a trend to the opposite direction, that is, to lower levels of cortisol and ACTH in the test. Moreover, one of the most consistent findings in the literature related to Dex/CRH test is the association between persistent HPA hyperactivity and higher rates of relapse. Zobel et al. [97] have described a cohort of patients undergoing Dex/CRH test on two different moments- after starting the first antidepressant treatment and a few days before the discharge. The authors found that those patients who had an increase in cortisol levels after Dex/CRH test between admission and discharge tended to relapse during the follow-up period, whilst those who showed a decrease in post-Dex/CRH cortisol levels tended to remain clinically stable in the follow-up period. Although Heuser et al. [96] reported that the sensitivity of this test is above 80%, depending on age and gender, the findings of HPA axis hyperactivity in the test have not been consistently confirmed in a series of other studies that investigated different subtypes of depression. Nevertheless, Dex/CRH test remains limited by the feature of dexamethasone pharmacokinetics and the lack of MR receptor activity assessment.

Recently, a suppressive test using another synthetic glucocorticoid, prednisolone, has been developed by Pariante et al. [93]. The prednisolone test (PST) also assesses MR. Prednisolone is a synthetic glucocorticoid similar to cortisol concerning its pharmacokinetics and pharmacodynamics features. In particular, its capacity of binding to MR as well as its half-life are similar to those of cortisol. However, the most important of these similarities is that prednisolone and cortisol are similar in their abilities to bind and activate MR as much as GR, especially when compared to dexamethasone [86, 93]. In studies examining human GR, prednisolone showed an affinity two-fold higher than that of cortisol, while dexamethasone has an affinity seven-fold higher than that of cortisol [100]. When Ballard et al. [101] examined mice GR, prednisolone presented the same relative potency as corticosterone to activate GR, while dexamethasone presented an affinity four-fold higher relative potency than that of corticosterone. Current evidence suggests that PST, in contrast to DST and Dex/CRH test, probes both MR and GR, and, hence, provides a betterphysiological measure of suppression [93]. See Fig. 2.

In three studies using PST, Juruena et al. [102-104] showed that patients with depression have marked hypercortisolism both before and after administration of prednisolone, but a similar percentage of suppression of salivary cortisol when compared to healthy controls. These data suggest that in patients with severe depression, the HPA axis activity is reset at a higher level, although feedback remains intact. Also, compared patients with a control group in both DST and PST [104]. After DST, depressed patients showed a weaker suppression than controls, however, these same patients who are resistant to dexamethasone, showed normal suppression after prednisolone; in other words, the same degree as shown by the control group. Furthermore, in controls, there was a correlation between suppression by prednisolone and suppression by dexamethasone,

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**Table 1.** Mineralocorticoid (MR) and Glucocorticoid (GR) Receptors according to their characteristics and attributions.

<table>
<thead>
<tr>
<th></th>
<th>MR</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INTERPRETATION OF ENVIRONMENTAL EXPOSURE</strong></td>
<td>Basil</td>
<td>Stressful</td>
</tr>
<tr>
<td><strong>PLASMA CORTISOL LEVEL</strong></td>
<td>Lower</td>
<td>Moderate to higher</td>
</tr>
<tr>
<td><strong>CORTISOL AFFINITY</strong></td>
<td>Higher (K&lt;sub&gt;D&lt;/sub&gt; = 0.5nM)</td>
<td>Lower (K&lt;sub&gt;D&lt;/sub&gt; = 5.0 nM)</td>
</tr>
<tr>
<td><strong>LOCATION OF CORTISOL RECEPTORS IN THE BRAIN</strong></td>
<td>Diffuse</td>
<td>Limbic system, and cortical and subcortical brain structures</td>
</tr>
<tr>
<td><strong>FUNCTIONS</strong></td>
<td>Stabilization of excitability; response system sensitive to stress; proactive feedback; selection of behavioral response; attention.</td>
<td>Suppression of increased excitability; recovery from stress-induced activation; reactive stress; facilitation of memory storage.</td>
</tr>
<tr>
<td><strong>AGONISTS</strong></td>
<td>Aldosterone, fludrocortisone</td>
<td>RU26752, spironolactone</td>
</tr>
<tr>
<td><strong>ANTAGONISTS</strong></td>
<td>Dexamethasone, RU28362</td>
<td>RU 38486</td>
</tr>
</tbody>
</table>

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The table above shows the differences in the characteristics and attributions of MR and GR receptors. The table includes information about the interpretation of environmental exposure, plasma cortisol level, cortisol affinity, location of cortisol receptors in the brain, functions, agonists, and antagonists.
indicating that GR and MR are equally sensitive. In contrast, no such correlation was present in depressed patients, confirming the dissociation between sensitivity to prednisolone and resistance to dexamethasone in depression. These data suggest the presence of a selective impairment of GR sensitivity, while MR sensitivity is maintained.

Regarding the studies that used neuroendocrine tests to investigate the relation between ELS and depression, they presented inconsistent results, and most part of them were restricted to assessment of GR by DST and Dex/CRH test [70, 73, 105-108].

The studies with Dex/CRH test are controversial. While some studies found lower levels of plasmatic cortisol and increased GR activity in individuals with ELS [70, 73, 108], others showed non-suppression by Dex/CRH test [106, 107]. Although the results are divergent, there seems to be an agreement about the association between abnormalities in GR activity in response to the Dex/CRH test in patients with ELS, suggesting decreased of GR activity in these patients. According to Tyrka et al. [107], individuals who experienced prolonged separations, abandonment or death of parents during childhood, also present increased cortisol response to Dex/CRH alterations. An association between HPA axis activity in individuals with ELS and psychiatric disorders in adulthood has been suggested by Heim et al. [105]. The results of this study indicate that men with a history of childhood trauma exhibited increases in ACTH and cortisol responses to Dex/CRH compared to non-abused men. In particular, abused men with current depression showed increased responsiveness, compared to control subjects and depressed men without childhood abuse experience. Increased response was associated with the severity, duration, and earlier onset of the abuse. Thus, these authors suggest that stressful events early in life can have a significant etiologic role in the HPA abnormalities found in people with psychiatric disorders [105]. About some studies that used DST, data are also controversial. Vreeburg et al. [109] found no influence of ELS on the HPA axis response to DST in depressed patients, while Newport et al. [105] found lower levels of cortisol and ACTH, and increased GR activity in women with depression and ELS. The effect of ELS on the HPA axis was also assessed by Juruena et al. [102,104] in two studies using PST. The study from 2006 assessed the HPA axis using both DST and PST, while the 2009 study only PST was used. They didn’t show any significant difference in the capacity of suppressing cortisol after prednisolone when comparing depressed patients with and without ELS.

To better investigate the connection between depression and GR, some researchers have used genetic and molecular tools to assess GR and related polymorphisms. NR3C1 is the exon 1F of human GR gene (NR3C1). Many polymorphisms of this gene alters GR function and have been studied in relation to depression and other psychiatric disorders. The GR single nucleotide polymorphism (SNP) rs10052957 has been associated with abnormal DST results [110-112]. Oberlander et al. [113] observed the relationship between prenatal exposed to maternal altered behavior, consequence of mood disorder and the methylation status of a CpG-rich region in the promoter and in NR3C1 in newborns, which were examined when they were three-months old. The results suggest that due the increased NR3C1 methylation at this site and the increased salivary cortisol stress, the newborn is sensitive to prenatal maternal mood and to a potential epigenetic process that links antenatal maternal mood and altered HPA stress reactivity during infancy. Still, ELS is associated with long-term effects on behavior and epigenetic programming of NR3C1 gene in human and in murine hippocampus. McGowan et al. [114] studied the epigenetic regulation of GR in the human brain associated with childhood abuse. They observed DNA methylation profiles spanning 6.5 million base pairs centered at the NR3C1 gene in the hippocampus of whom experienced abuse as children and non-abused controls, also comparing these data to DNA methylation profiles in rats that received differential levels of maternal care. The obtained results
support the concept of an analogous cross-species epigenetic regulatory response at the level of the genomic region to ELS.

GR can also have its activity or expression compromised by the presence of polymorphisms in a gene called in a co-chaperone immunophilin FK506 binding protein 5 (FKBP5) - gene product forms part of a complex with GR and can modulate cortisol-binding affinity [115, 116]. GR is regulated by FKBP5. Supriyanto et al. [116] observed that haplotypes in FKBP5 gene are associated with completed suicide in Japanese population. Corroborating with these data, White et al. [117] observed the relationship of haplotypes with risk alleles. There, they observed increased amygdala reactivity in the context of higher emotional neglect, one of the ELS subtypes, suggesting that increased threat-related amygdala reactivity may represent a mechanism linking psychopathology to interactions between common genetic variants affecting HPA axis function and childhood trauma. Yet, considering that variations in FKBP5 have been associated with increased recurrence of depression and with rapid response to antidepressant treatment, Willour et al. [115] decided to determine whether common FKBP5 variants confer risk for BD. They found that genetic variation within FKBP5 may influence attempted suicide and number of depressive episodes in bipolar subjects.

MINERALOCORTICOID RECEPTOR

Several studies have documented the importance of MR in stress regulation [87, 118]. In this context, some studies have used MR agonists and antagonists to assess their function in healthy subjects. Otte et al. [119] and Buckley et al. [120] evaluated the effect of one MR agonist, fludrocortisone, in nocturnal activity of the HPA axis in healthy subjects. They found that fludrocortisone decreased average cortisol levels, causing inhibition of MR nocturnal activity. Assessing MR function in the HPA axis by administering spironolactone (MR antagonist), many studies observed a significant increase in cortisol concentrations [83, 100, 121, 122]. Therefore, these studies suggest an important role of MR in HPA axis regulation, showing significant clinical implications for better understanding depression.

Reported data about the role of MR in depression are still controversial. While some studies showed increased MR activity in depression, others showed reduced MR function. For example, Wang et al. [123] found MR gene expression upregulated in the hypothalamus of depressed patients, while Yau et al. [124] observed MR downregulated in subjects' hippocampus in response to antidepressants, suggesting that blocking MR might be promising from a therapeutic perspective. Otherwise, there are also studies showing that depressed suicide victims have decreased production of hippocampal MR mRNA compared to healthy controls [125].

Some studies have been published using challenges that assess, preferentially, MR function in depression. They used fludrocortisone (MR agonist) or spironolactone (MR antagonist). These studies are still scarce and reveal unclear results. Spironolactone is able to activate the HPA axis, blocking the feedback mediated by MR. Young et al. [126] observed significant increase of cortisol levels in patients treated with spironolactone. These authors suggest that MR activity is increased in patients with depression compared to controls, and that depression is accompanied by a shift of balance between GR and MR [126]. Thus, recently, we have published a study probing the HPA axis response to MR stimulation in depressive patients with and without ELS [75]. Our findings indicate that patients with ELS show suppression of salivary cortisol levels after fludrocortisone (MR agonist) and dexamethasone (GR agonist). That is, patients with ELS are equally sensitive to both GR and MR. On the other hand, in depressed patients without ELS and in controls, such suppression after fludrocortisone administration was not found. Patients without ELS and controls showed only suppression by dexamethasone. Our data indicate differences in HPA axis functioning between depressed patients with and without ELS, suggesting the former to be more sensitive to a MR agonist than the latter. Thus, these findings suggest that ELS contributed to the impairing of MR function.

MR polymorphisms have been studied, and their association HPA axis function, depressive disorders and stress profiles. The most currently studied MR polymorphisms are located in the exon 2 of MR gene (Nr3c2): rs5522 (MR180V) and rs2070951 (-2G/C). These two polymorphisms have been associated to a higher frequency of depressive symptoms in elderly [129], to neurotic disorders in depressive adults [130], and to differences in the CAR, dependency and dexamethasone treatment or on the interaction with selective serotonin reuptake inhibitors (SSSR) [131, 132]. In healthy subjects, these two single nucleotide polymorphisms (SNPs) were related to differential neuroendocrine and sympathetic responses to psychological stressors [110, 112, 131-133]. Finally, Klok et al. [132] examined MR haplotypes protection against depression, and observed that functional SNPs in exon 2 are linked to SNPs in MR promoter region, which potentially influence MR transcription and its dynamic expression, enhancing resilience to depression, particularly in women.
CONCLUSION

Overall, the reviewed evidence supports the hypothesis that an imbalance in MR and GR functioning may be a risk factor for depression. Moreover, results from studies examining the relationship between ELS and HPA axis indicate that ELS, in combination with genetic background, seems to sensitize certain circuits in the brain and lead to persistent alterations in reactivity and sensitization of the HPA axis to subsequent stress, reflected in an altered MR/GR balance, which contributes to the risk for depression.

However, in the investigation of ELS and depression, most studies used tests for assessing the HPA axis preferentially assessing GR. Thus, the role of MR in regulating the inhibitory feedback in HPA axis and the changes that ELS generates on it need further elucidation. In particular, probes that assess functioning of both GR and MR should be used.

A better understanding of the mechanisms by which exposure to ELS leads to HPA impairment and vulnerability to depression will allow for the new approaches to early intervention, including, among others, targeted pharmacologic and psychoeducational strategies. Future studies should approach risk factors for depression from different levels of theoretical integration taking into full account the environment versus gene interaction.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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