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# HPA Axis Modulation in the Treatment of Mood Disorders

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## 1. Introduction

### 1.1. The Hypothalamic-Pituitary-Adrenal (HPA) axis

The primary regulator of the mammalian stress response is the hypothalamic-pituitary-adrenal (HPA) axis. Corticotrophin-releasing factor (CRF), a 41 amino-acid containing neuropeptide, is the major physiological mediator of the HPA axis. CRF is synthesized in parvocellular neurons of the hypothalamic paraventricular nucleus (PVN). These neurons project to the median eminence where CRF, together with arginine vasopressin (AVP), is released into the hypothalamic-hypophyseal portal circulation to act on corticotrophs of the anterior pituitary. Activation of these cells, leads to the synthesis and release of adrenocorticotrophic (ACTH) hormone. ACTH is released into systemic circulation and acts on the adrenal cortex resulting in the synthesis and secretion of cortisol. Cortisol, the main glucocorticoid in primates, mobilizes energy stores in response to a threat. Additionally, cortisol regulates the release of CRF, AVP and ACTH through negative feedback via glucocorticoid receptors in the hypothalamus and pituitary mineralcorticoid receptors in the hippocampus.

CRF, first isolated by Vale *et al.* in 1981, is released in response to stress not only in the hypothalamus but in other subcortical regions as well, including the central amygdala (CeA) [1]. Although hypothalamic CRF release occurs in response to all types of stress, the central amygdale (CeA) CRF is believed to mediate a large proportion of the emotional component of stress. CRF release produces multiple effects in the body including alterations in metabolic rate, changes in sympathetic output, modulation of emotional state and regulation of appetite and reproductive status [2-5]. A great deal of evidence suggests that CRF coordinates the endocrine, autonomic, immune and behavioral responses to stress. Adaptation to acute verses chronic stress also appears to play a significant role. Chronic stress is associated with a number of health conditions including heart disease, infertility and mood disorders [6].

CRF binds to a family of CRF receptors, of which two have been identified in humans, CRF 1 and CRF 2. Both receptors are 7-transmembrane G-protein coupled receptors that share a 70% sequence homology. The CRF 1 receptor, first cloned in 1993, contains 415 amino acids and is widely expressed throughout the CNS. It is thought to be the receptor mediating the direct action of CRF on the HPA axis. Additionally, the CRF 1 receptor is highly expressed in the cerebellum, hippocampus, amydala, pituitary and throughout the cerebral cortex. The CRF 2 receptor is structurally similar to the CRF 1 receptor with a few noticeable differences. The CRF 2 receptor is poorly expressed in the anterior pituitary, but is highly expressed in the CNS lateral septum, ventromedial nucleus of the hypothalamus, the cerebral cortex, olfactory bulb, amygdala, dorsal raphae nuclei and bed nucleus of stria terminalis.

Although CRF was the first endogenous ligand described to act upon the CRF receptors, others have subsequently been identified. CRF binds to the CRF 1 receptor and is thought to act on the corticotrophs regulating HPA activity. CRF is expressed both peripherally as well as in the CNS with highest expression in the hypothalamus, amygdala, cerebral cortex and septum. Urocortin 1, a 40 amino acid peptide sharing 45 % homology to human CRF, has high affinity to both the CRF 1 and CRF 2 receptors [6]. Urocortin 1 is found in highest concentration in the Edinger-Westphal nucleus and the hypothalamus but overall, its expression is more widespread peripherally in the GI tract, testes, heart, thymus, spleen and kidney. Urocortin 2 (stresscopin-related peptide), a 38 amino acid peptide, has a high affinity for the CRF 2 receptor suggesting that it may be a primary ligand. Urocortin 2 is found in highest concentration within the hypothalamus, locus ceruleus and brain stem nuclei. Urocortin 3 (stresscopin), a 38 amino acid peptide with 40% homology to Urocortin 2, also appears to be selective for the CRF 2 receptor and is mainly expressed in the amygdala, hippocampus and brainstem [6]. The HPA system is further regulated by the CRF binding protein (CRBP), which binds to CRF and Urocortin 1 in the extracellular fluid and plasma thus sequestering them and preventing CRF receptor binding. Interestingly, Urocortin 2 and 3 have little affinity for CRFBP and therefore may be regulated through a different mechanism. In general, activation of CRF receptors by either CRF or Urocortins leads to a G protein coupled activation of adenylate cyclase , cAMP production and c-fos activation in most cell types, though co-activation of additional pathways have been reported [144]. In corticotrophs, CRF binds to CRF 1 receptors causing co-activation of both calcium pathways and protein kinase A (PKA) pathways leading to phosphorylation of extracellular regulated kinases (ERK) 1 and 2. It is notable that injections of CRF into limbic areas does not lead to ERK phorphorylation which suggest that other downstream responses may regulate extrahypothalamic sites.

## 2. The HPA axis in mood disorders

There is much evidence demonstrating that components of the HPA axis play a role in the pathogenesis of affective disorders including depression. One notable early study was performed by D.J. McClure and colleagues in 1966 in which he demonstrated increased cortisol levels in the urine of depressed patients [7-8]. Later studies have confirmed these

results and extended the findings by documenting that MDD patients have increased cortisol concentrations in the urine, blood and cerebrospinal fluid (CSF). This elevation in cortisol generally occurs immediately preceding or during the onset of mood symptoms. However, hypercortisolemia is considered a state rather than a trait marker for depression and thus lacks specificity as a biomarker for risks for mood disorders [9-13].

In addition to cortisol, other HPA hormones have been found to be dysregulated in depression and chronic stress. CRF, ACTH and AVP have consistently shown dysregulation in mood disorders. In 1984, Nemeroff et al. reported an increase in CRF concentrations in CSF of untreated depressed patients, which has been confirmed in a number of studies [14-16]. CRF signaling is overactive in major depressive disorder, both in regards to HPA and extrahypothalamic function [145]. Laboratory animal studies that utilize brain-region specific microinjections of CRF have shown behavior responses reminiscent of major depression in humans including increased anxiety, changes in slow wave sleep, anhedonia, decreased appetite and diminished libido. Elevated cerebrospinal fluid (CSF) concentrations of CRF are observed in many MDD patients, thought to reflect hyperactivity of the hypothalamic and extrahypothalmic CRF producing regions [20]. Examination of post-mortem tissue of depressed subjects reveals increased CRF mRNA expression in the PVN, locus ceruleus and prefrontal cortex, a finding that supports CRF hyperactivity. Autoradiographic studies reveal a 23% decrease in CRF 1 receptor binding sites within the frontal cortex of suicide victims [17-18], reflecting a downregulation of the system most likely secondary to chronically high levels of CRF. It is hypothesized that downregulation of CRF receptors is deleterious to the disease pathophysiology in depression because negative feedback regulation likely occurs in the brain. Thus without feedback inhibition, there is an inability to shut off the HPA axis, including CRF overproduction in both the hypothalamus and other regions such as the central amygdala. Further evidence for hyperactivity of CRF containing circuits in depression is provided by several studies that have revealed that patients in the recovery stages of MDD who maintain elevated CSF CRF concentrations despite their euthymic state are predisposed to early relapse of depression. Similarly patients who exhibit improvement in depression symptoms without concurrent normalization of the DEX/CRF response are more likely to relapse [26]. Currently available antidepressants, while exerting their primary pharmacological effect on monoamine systems, also reduce HPA responsiveness. Treatment of depressed patients with a selective serotonin reuptake inhibitor (SSRI) and electroconvulsive therapy (ECT) leads to reductions in CSF CRF concentrations. This data is concordant with the hypothesis that CRF/HPA axis normalization is associated with symptom resolution.

Although CSF CRF levels are often elevated in depressed patients, it is not a reliable biomarker for mood disorders [20]. The CRF stimulation test is a more accurate measure of HPA axis activity than CSF CRF concentrations in part because the latter represent contributions of both hypothalamic and extrahypothalamic circuits. In the CRF stimulation test, intravenously administered CRF (which does not enter the CNS) elevates plasma ACTH and cortisol concentrations by stimulating the CRF 1 receptors in the anterior pituitary. In normal patients, ACTH and cortisol concentrations increase

predictably. MDD patients as a group demonstrate a blunted ACTH response in this test, most likely due to chronic CRF hypersecretion and negative feedback and cortisol hypersecretion at the pituitary corticotrophs [21-23]. Another even more sensitive test of HPA axis activity is the DEX-CRF test [24-25]. In this test, dexamethasone (DEX) is administered the evening before CRF. In normal controls without depression, DEX suppresses ACTH and cortisol secretion via negative feedback to the pituitary. In MDD patients, feedback inhibition is blunted by the presence of elevated cortisol, therefore little suppression takes place and ACTH levels remain high. CRF administered to healthy patients the next morning will show little or no increase CRF or ACTH due to the effect of DEX suppression. On the contrary in MDD patients, DEX does not suppress ACTH secretion and ACTH and cortisol levels increase. This suggests that both CRF overexpression and glucocorticoid insensitivity contribute to the hyperactivity of the HPA in depression. The sensitivity of the DEX-CRF test can predict 90% of MDD patients correctly and can even have utility in identifying asymptomatic remitted patients who continue to exhibit HPA axis dysfunction and are at risk for relapse [26].

A second line of research that supports the link between HPA axis dysfunction and depression is found in studies that associate early life stressors with subsequent changes in neuroendocrine function. A series of clinical studies suggest that childhood trauma in humans is associated with sensitization of the HPA axis, glucocorticoid resistance, increased CRF activity, immune activation and reduced hippocampal volume, closely paralleling the neuroendocrine features of depression.[40-41]. Early life stressors, such as child abuse and neglect, influence CRF neuronal activity and HPA functioning during development and lower the individual's threshold to develop depression. Heim et al. reported that depressed women with and without childhood abuse and nondepressed women with childhood abuse exhibited blunted cortisol responses in a standard ACTH stimulation test [40-41]. Decreased cortisol response under conditions of chronic stress might result in a relative lack of cortisol regulation at the CNS level. Upon further stress, such women may then repeatedly hypersecrete CRF, eventually resulting in pituitary CRF receptor downregulation and symptoms of depression through CRF effects on extra-hypothalamic circuits. The hippocampus is critically involved in the control of the HPA axis as well as explicit memory and contextual aspects of fear conditioning. Stress and glucocorticoid overexposure have adverse effects on the CA3 region of the hippocampus resulting in loss of dendritic spines, reduction in branching and impairments in neurogenesis [35,143]. Furthermore, patients with MDD and PTSD exhibit decreased hippocampal volumes. Heim et al. found that the left hippocampus was 18% smaller than in non-abused depressed women and 15% smaller than non-abused controls. It appears that a smaller hippocampal volume in major depression is associated with childhood trauma and is not observed in depressed patients without such trauma, paralleling neuroendocrine findings. [39-41]

Genetic studies focusing on single nucleotide polymorphisms (SNPs) in the CRF system have shown susceptibility or resilience to developing depression as well as variation in response rates to antidepressants. Multiple studies have examined the effect of SNPs in the CRF system. Binder et al. described an association of SNPs within the CRF system and

remission and response rates to antidepressant treatment in the STAR*D sample [57]. A genetic variant within the corticotrophin releasing hormone binding protein (CRHBP) locus affects response to citalopram in African American and Hispanic patients, suggesting a role for this gene and the CRF system in antidepressant treatment response. Van Rossum et al. described carriers of a rare polymorphism in the glucocorticoid receptor gene ER22/23EK as demonstrating a more robust response to antidepressants. Ressler et al. reported that variants in the serotonin transporter-linked polymorphic region (5-HTTLPR) interacts with CRF 1 receptor gene (CRHR1) and child abuse to predict current adult depressive symptoms (i.e. gene x gene x environment) [145]. These data indicate that individuals carrying the risk alleles in both genes exhibited clinically relevant depressive symptoms at less severe levels of child abuse than individuals with no or only one of the risk alleles. Heim et al. scrutinized variations of the CRHR1 gene and the development of depression in childhood trauma. The allele rs110402 SNP was associated with decreased symptoms of depression among male subjects exposed to moderate-severe childhood abuse exposure, whereas this protective effect is not observed in female subjects with childhood abuse exposure.

## 3. Non-mood related effects of HPA-axis hyperactivity

HPA axis hyperactivity can have a significant impact on an individual's physical health aside from the effects directly related to mood disorders. Although we will not review this literature because it is not a focus of this chapter, such adverse effects often additionally complicate mood disorders. Clinical studies indicate that the prevalence of depression in patients with cardiovascular disease can be as high as 1 in 3 [27-28]. Chronic mood disorders are a risk factor as threatening as high fat diets or cigarette smoking to cardiovascular health. Depressed patients often suffer higher rates of cardiovascular disease, perhaps due in part to chronic dysregulation of the HPA axis. It is therefore of major importance that modulators of the HPA axis may be advantageous not only in regards to treatment of mood disorders, but for their potential to diminish the systemic effects of depression including heart disease, obesity, osteoporosis and immune system dysfunction.[6]

## 4. Modulation of the HPA axis as a therapeutic strategy to treat mood disorders

Based upon the preponderance of data linking HPA axis hyperactivity to mood disorders, it is reasonable to assume that CRF/ACTH/cortisol and their receptors are pathologically involved in the neurobiology of depression. Taking this into consideration, efforts have been made to identify critical components of the HPA axis a properly designed drug could exert a therapeutic action. One of the most promising targets in recent years has been the CRF receptors. CRF receptors are G protein coupled receptors which are present in humans in two forms, CRF 1 and CRF 2. The CRF 1 receptor exists in multiple isoforms (ie. CFR 1a-CRF 1h) with the CRF 1a subtype being the best known and most functional isoform. The CRF 1 receptor is predominantly located in the CNS and controls HPA axis activity. [2, 29] The CRF 2 receptor has three known functional subtypes in humans (ie. CRF 2a, CRF 2b,

CRF 2c). The CRF 2 receptor has a higher affinity for Urocortins than CRF, and is thought to mediate the peripheral effects of stress [4]. When considering a modulator, it is interesting to speculate on both receptor subtypes, but in actuality, therapeutic development has focused solely on the CRF 1 receptor. Antagonism of the CRF1 receptor should theoretically decrease basal and stress induced increases in HPA axis activity, reduce the health-related side effects of depression and improve the treatment of mood disorders. The most convincing data supporting CRF 1 receptor antagonists comes from animal models. CRF1 receptor knockout mice demonstrate a large reduction in ACTH, decreased stress-induced glucocorticoid secretion and reduced anxiety [30-32]. There have been several attempts to develop clinically useful CRF 1 receptor antagonists to treat mood disorders, with minimal success. It is important to note that in terms of mood and anxiety symptoms, CRF 1 receptor antagonists are believed to act on extrahypothalamic/extrapituitary sites. This has been well documented in preclinical studies. In fact the CRF1 receptor antagonists exhibit anxiolytic and antidepressant effects even in hypophysectomized animals [33-34].

Antidepressant-induced HPA axis normalization may be attributable to some improvement in depressive symptoms. Currently available antidepressants reduce the overall responsiveness of the HPA axis and the activity of hypothalamic and extrahypothalamic CRF neurons. This is supported by the fact that chronic antidepressant administration results in reductions in CRF mRNA expression and CRF concentrations [143]. In laboratory animal studies, these changes followed depressive symptom resolution supporting the hypothesis that normalization of CRF transmission plays a vital role in the mechanism of action of antidepressants. In rats treated with the antidepressant tianeptine (approved in Europe for depression and anxiety), decreased CRF concentrations were noted in the rat hypothalamus, as well as decreased ACTH concentrations in the anterior pituitary. Numerous connections between the neuropeptide circuit and the CNS monoamine system suggest that elevations in CRF activity might alter monoamine signaling. For example reserpine, an agent that causes monoamine depletion and depression in vulnerable individuals, also increases CRF release from the rat hypothalamus and posterior pituitary [143].

During a depressive episode, hypersecretion of CRF in the CNS likely increases locus cerulous (LC) activity through a CeA-LC connection. Reciprocal noradrenergic projections from the LC to the amygdala activate CRF-containing cells [19]. Elevated noradrenergic transmission in depression may indirectly contribute to symptoms secondary to increased activity of CeA CRF. Noradrenergic neurons from the LC also project to the dorsal raphe nucleus (DRN) to increase serotonergic activity and project back from the DRN to decrease noradrenergic firing. [143] One hypothesized mechanism of action of SSRIs is that by increasing serotonin availability, SSRIs subsequently decrease activation of the LC and in turn decrease amygdalar activation of CRF. Additional animal studies have shown that chronic imipramine and desipramine administration in rats increases CRF binding in the CNS as well as other brain regions. Such increases in the density of CRF 1 receptor binding sites are likely secondary to antidepressant induced reductions in CRF-ergic activity. Furthermore, chronic administration of venlafaxine has been shown to reduce hypothalamic

CRF responsiveness to stress as well as blocking stress-induced elevations in CRF mRNA expression in the PVN [143].

## 5. CRF1 receptor antagonists in mood and anxiety disorders

Since Vale first isolated CRF in 1981, CRF receptor antagonists have been sought for the treatment of not only depression but for anxiety, addiction and irritable bowel syndrome [1]. In 2000, Zobel et al. published the first small clinical trial of a CRF1 receptor antagonist for the treatment of mood disorders [35]. In this open-label trial, doses of R-121919 were titrated up to 80 mg and produced an antidepressant effect equivalent to the SSRI paroxetine. There was no decrease in basal plasma ACTH or cortisol levels, which lessened concern that CRF 1 receptor antagonists might produce a state of adrenal insufficiency. To date, there are more than 28 clinical trials in the peer reviewed literature that address the potential utility of CRF 1 receptor antagonists for the treatment of anxiety and mood disorders [4].

Animal models have repeatedly shown that non-peptide CRF 1 receptor antagonists produce anxiolytic effects in rodents. For example, these agents have been shown to reduce conditioned fear, shock-induced freezing, defensive burying behavior, acoustic startle response and anxiety-like effects from neonatal isolation [4]. Positive findings in animal models include a few notable studies. In 2004, Nielsen et al. demonstrated that treatment with DMP696 and R121919 reduced forced swim immobility (a genetic model of depression) in mice [146]. Similarly Chaki et al. showed that olfactory bulbectomized rats, a putative model of depression, reduced hyperemotionality when treated with R278995 [147]. Improvement in coat appearance and reversed reductions in hippocampal neurogenesis were found in mice chronically treated with antalarmin or SSR125543A [4]. Unfortunately several animal studies produced negative findings in regards to screening tests for antidepressant activity. Jutkiewicz et al. found that CP-154526 and R121919 failed to reduce swim immobility in rats [148]. Similarly, acute treatment with CP-154526 which was initially reported to produce antidepressant-like effects in the learned helplessness paradigm was later found to be unsubstantiated [4]. A potential explanation for these mixed findings is that CRF 1 antagonists might only exhibit antidepressant properties in certain animal models or particular endophenotypes. Support for this explanation is found in studies that show CRF 1 antagonists differentially reduce anxiety behaviors in high anxiety models and reduce ethanol intake in dependence models rather than in healthy animals.

Paralleling the mixed results in animal models, many of the better-powered clinical trials have been disappointing by revealing a lack of efficacy for CRF1 receptor antagonists in patients with MDD. A 6-week randomized, placebo controlled trial in 2005 compared CP-316,311 to placebo and sertraline in 128 patients with major depressive disorder. The trial, however, was terminated early due to no significant antidepressant effect of the CRF1 antagonist compared to placebo [36-37]. In the largest study to date (n=260), Coric et al. conducted an 8-week multicenter, randomized, double-blind, placebo-controlled clinical trial with Pexacerfont (BMS-562,086) for generalized anxiety disorder. No significant

anxiolytic effect was observed compared to placebo though the comparator in the study, escitalopram, was efficacious [38-39]. It is important to note that these studies have not used narrowly defined patient sub-types such as psychotic, anxious or atypical depression, but instead have utilized the broader MDD inclusion criterion. Considering the fact that there is overwhelming evidence that CRF is hypersecreted in depressed patients with a history of childhood abuse and neglect, a clinical trial of CRF1 receptor antagonism in this discrete subset of patients with major depression would be of considerable interest [40-45].

Despite the above listed shortcomings, several pharmaceutical companies have developed viable clinical candidates. Several CRF 1 antagonists from different pharmaceutical companies have entered clinical trials since December 2004. Due to promising results with R121919 during an open-label Phase IIa trial, clinical anticipation has been high. However, R121919 development was discontinued shortly thereafter secondary to elevation of liver enzymes. Despite major efforts to the contrary, no subsequent CRF 1 antagonist has successfully completed a definitive Phase III trial. Currently, the number of additional CRF 1 antagonists that are undergoing or have completed efficacy trials is two for social anxiety disorder (GSK561679, GW876008), and three for depression (GSK561679, GW876008 and Pexacerfont) [4]. Apparently the results from these trials in the treatment of anxiety and depression have been uniformly negative.

## 6. CRF-2 receptor antagonists in the treatment of mood disorders

CRF 2 receptor knockout mice have revealed inconsistent findings in regards to anxiolytic behaviors and sensitivity to stress [48-51]. Several studies to date suggest a contribution of the CRF2 receptor to HPA axis regulation and mood disorders. There is evidence that the CRF 2 receptor helps to modulate the duration of the HPA response to stress. By blocking the CRF 2 receptors in humans, the HPA axis response could potentially be more quickly terminated after a stressful event. To date, there are no studies examining early attenuation of the HPA axis following stressful situations. The best candidates for CRF 2 receptor antagonists at this time are antisauvagine-30, astressin-2B and K41498, all of which are peptide based and thus have limited therapeutic efficacy [46-52].

## 7. CRF binding protein

The CRF binding protein (CRF-BP) is a 37-kDa glycoprotein which is present in interstitial spaces and plasma. Its primary function is to bind CRF and Urocortin 1 to reduce their bioavailability and prevent binding to the CRF receptors [53-54]. To our knowledge, CRF-BP has received little attention as a novel therapeutic target for drug development and treatment of mood disorders despite its regulatory function in the HPA system [56]. Binder et al. studied patients from the STAR*D sample and found a SNP within the CRHBP locus (rs10473984) that was significantly associated with glucocorticoid-receptor resistance and higher HPA axis hormone levels [57]. This SNP significantly reduced both remission and reduction in depressive symptoms in response to citalopram. In a study of post-mortem

brain tissue of bipolar and schizophrenic patients, CRF-BP mRNA expression was found to be decreased possibly indicating increased CRF availability [55]. It is important to note that some evidence exists that increasing CRF-BP could potentially modulate the HPA axis. It is feasible to propose that by increasing the CRF-BP (i.e. through administration, genetic up-regulation, microRNA targeting) and decreasing the bioavailability of CRF, HPA hyperactivity may be attenuated [58-59].

## 8. Arginine vasopressin 1b receptors

Arginine vasopressin (AVP) is a peptide hormone produced in the both the magnocellular and parvocellular neurons in the hypothalamus but released through two different mechanisms. AVP produced by the magnocellular neurons travels through the infundibulum to the posterior pituitary where it is stored until release. AVP synthesized by the parvocellular neurons is released into the median eminence and travels via hypophyseal portal circulation to the anterior pituitary where it stimulates corticotrophs. The primary function of AVP is to regulate extracellular fluid volume via its action on the V2 receptors (V2R) located on the renal collecting ducts; thus absorbing water and decreasing urine formation.

AVP and AVP receptor activation, however, can produce a number of CNS and peripheral effects and have been postulated to play a role in mood disorders [60-61]. AVP that is released from the parvocellular neurons travels to the anterior pituitary to act on AVP1b receptors and enhances the release of CRF and ACTH. This pathway has the potential to be a modulation point in the treatment of mood disorders. For example, SSR149415, a potent and selective AVP1b receptor antagonist has been proposed as a novel antidepressant and has been tested in clinical trials for the treatment of major depression. However, the clinical trial was discontinued in 2008 for undisclosed reasons [62, 62]. A great deal of interest still surrounds AVP 1b receptor antagonist development with future compounds possibly acting in synergistic ways with CRF 1 antagonist.

## 9. Anti-glucocorticoid therapy for mood disorders

Hyperactivity of the HPA axis has been repeatedly demonstrated in patients with psychotic depression. Early studies have shown that patients with psychotic depression have high rates of dexamethasone nonsuppression in the DST and abnormal diurnal fluctuations of cortisol [64-65]. It has been hypothesized that high concentrations of cortisol in psychotic depression lead to hyperactivity of dopamine neurons thus worsening the psychosis [66]. Adopting this hypothesis, it is feasible that one therapeutic modality in the treatment of psychotic depression would involve using agents that block the synthesis of cortisol. Several types of anticortisol agents have been investigated in psychiatric disorders. These include cortisol synthesis inhibitors (ie. ketoconazole, metyrapone, aminogluthethamide), CRF receptor antagonists and glucocorticoid receptor antagonists such as mifepristone. Ketoconazole, an antifungal agent, has been used in clinical trials with varying amounts of

success. For example, Wolkowitz et al. found that ketoconazole was associated with significant antidepressant effects in patients with depression and baseline hypercortisolemia [149]. While the majority of studies have suggested that cortisol synthesis inhibitors have antidepressant benefits, conclusions are limited due to small sample sizes. Complicating the issues further are the potential side effects of ketoconazole administration which include decreased androgen and aldosterone synthesis, nausea, vomiting and occasionally hypoadrenalism and hepatotoxicity.

The brain is an important target organ for corticosteroids. Both high-affinity mineralocorticoid receptor (MR) and lower affinity glucocorticoid receptor (GR) are highly expressed in specific brain regions including the CA1 hippocampus, dentate gyrus and basolateral amygdala [64]. Through an interplay with other stress hormones (CRF and norepinephrine), corticosteroids alter neuronal activity and play a key role in attention, vigilance, memory and behavioral adaption. Cortisol is similar in structure to the sex steroid progesterone as well as the potent progesterone antagonist, mifepristone (RU486). Mifepristone has a high affinity for progesterone and glucocorticord receptors. It is primarily used in the gynecological treatment of endometriosis, as contraceptive and for various progesterone sensitive tumors. It was recently FDA approved for the treatment of Cushing's syndrome. Mifepristone has the added advantages of having little to no effect on estrogen, monoamine, histamine, muscarinic or mineralocorticoid receptors. It appears to be well tolerated and has not been associated with adrenal insufficiency or heptatotoxicity. At high doses mifepristone antagonizes GRs, but not MRs, and there is considerable evidence that it has efficiency in the management of psychotic depression [67-72]. Van der Lely et al. first reported the psychotropic effects of mifepristone in 1991 citing a substantial resolution of psychosis and depression in 2 patients with Cushing Syndrome [150]. A possible mechanism of action for mifepristone is through potent antagonism of GRs, MRs are up-regulated, thus enhancing HPA feedback regulation. Several clinical trials have used mifepristone in the treatment of depressive disorders [73-74]. Murphy *et al.* completed an open label study of mifepristone 200mg/day in four nonpsychotic patients with chronic depression. Patients were treated for eight weeks with 3 out of 4 reporting improvements in depression as measured by the Hamilton Rating Scale for Depression (HAM D) score [67]. Due to the fact that psychotic depression exhibits the most consistent HPA dysregulation, Belanoff et al. examined the psychotrophic effects of mifepristone in a group of five patients with psychotic depression. In a double blind, crossover design, patients were treated for four days with mifepristone 600mg/day or placebo. All five patients showed substantial improvement in depression and 4 out of 5 experienced an improvement in psychosis [75-76]. As a follow up, this same group studied 30 additional patients with psychotic depression and used mifepristone in doses of 50, 600 or 1200mg/day for 7 days. Of the groups treated with 600+ mg/day, 30% had a decrease in psychotic symptoms as measured by the Brief Psychiatric Rating Scale (BPRS) [75-76]. Subsequent larger clinical trials, with 221, 258 and 443 patient cohorts were treated with placebo or mifepristone (doses 300-1200 mg/day) over 7 days. Results revealed a correlation between mifepristone plasma concentrations and

clinical improvement, which persisted for several weeks after mifepristone discontinuation [68, 69, 72, 77-79].

Since mifepristone has significant and potentially deleterious side effects associated with its affinity for the progesterone receptor, the development of more selective GR antagonists is of great interest. There have been reports of RU-43044, CORT-108297 and RU-43044 as possible candidates for selective GR antagonism. [80-84]

## 10. Glucocorticoid and mineralcorticoid receptor activation in the treatment of non-psychotic and anxious mood disorders

HPA axis feedback both in the brain and in the pituitary is achieved via cortisol activation of mineralcorticoid receptors (MR) and glucocorticoid receptors (GR). As noted above, the MRs have approximately ten times the affinity for circulating cortisol than the GRs. Thus, the GRs will only be occupied when the MRs are saturated. HPA feedback primarily occurs first at MRs in the hippocampus and then as cortisol levels increase further, GR are activated for additional feedback inhibition [85].

Due to the fact that non-psychotic patients tend to have an overactivity of the HPA axis with elevated cortisol levels, the MR feedback regulation system is likely already saturated thus making MRs a poor modulation point for therapeutic intervention. The GR system, due to its lower rate of activation and broader receptor distribution, makes a much better target for therapy. Traditionally, mood disorder patients display poor feedback regulation of the HPA axis via GRs [86-87]. Clinical studies have revealed polymorphisms of GRs and related molecules that are present in some mood disorders [88].

Several GR and MR specific agonists have been developed for potential treatment in mood disorders. The central idea of these agonists is to use them to potentiate the feedback inhibition of CRF and ACTH release thus reducing HPA axis tone. Endogenous glucocorticoids could serve as potential candidates due to their long plasma half life and penetration of the blood-brain barrier. Synthetic analogs of endogenous glucocorticoids (ie. dexamethasone and prednisone) may also serve as viable options. Dexamethasone (DEX) is a potent synthetic GR agonist that is 25 times more potent than cortisol [89]. Its main clinical use is for the treatment of various inflammatory syndromes. Arana et al. conducted a number of trials using DEX for the treatment of depression and bipolar disorder. In one of the studies 37 patients were treated for a 2 week period with DEX treatment showing superiority to placebo in reducing depressive symptoms [90-91].

DEX has also been studied for the treatment of anxiety disorders including PTSD. Several clinical studies have shown that patients with PTSD have lower cortisol levels, elevated CSF CRF levels and are more sensitive than normal volunteers to DEX suppression [42, 92]. Due to their low cortisol level and reduced capacity for GR feedback inhibition, administration of DEX could be helpful to regulate HPA activity in these patients. Early studies involving DEX treatment in a cohort of PTSD patients, one in combat veterans and the other in sexually abused adolescents, demonstrated reductions in ACTH levels after DEX

administration [93-94]. In 2011, Jovanovic et al. examined the effects of DEX on fear-potentiated startle (FPS) in 33 PTSD patients and 67 controls [95]. DEX administration was associated with reduced fear potentiated startle and was correlated with cortisol levels. Further studies need to be performed to examine if GR or MR agonists are playing a role in HPA axis regulation or is their beneficial effect due to extra-endocrine CNS effects.

Unfortunately the use of DEX, prednisone or other glucocorticoids is not without its limitations. Side effects including depression, mania, psychosis and delirium have all been reported even after a single dose [96]. Additionally, high dose corticosteroid administration increases the incidence of depression, anxiety and hypomania in medically ill patients [97-108].

## 11. FKBP5 as a genetically-linked HPA axis therapeutic target

A number of HPA axis genes have been identified and are speculated to play a role in the initiation of mood disorders [109-135]. It is therefore likely that genetic polymorphisms that affect the function of these genes may modulate an individual's response to treatment. For example, FKBP5 (a.k.a. FKBP51, FK506 binding protein 51, hsp58) is an immunophilin that works with hsp90 to regulate glucocorticoid receptor sensitivity has been genetically linked to anxiety, depression and PTSD [136, 137]. Briefly, hsp90 (along with numerous other proteins) act in the cell to assist with protein folding. Hsp90 action is supported by co-chaperones in the cell as well, one of these being FKBP5. In GR containing cells, hsp90 and FKBP5 both bind to the GR as chaperones during protein folding and maturation [137-139]. When the GR is bound with hsp90 and FKBP5, it becomes less sensitive to the presence of cortisol. Thus over expression of FKBP5 produces a significant reduction in cortisol action at GRs [137-140]. Additionally, FKBP5 is upregulated by GR activation, suggesting that FKBP5 is an intracellular negative feedback protein [141-142]. Therefore, it is not surprising that FKBP5 polymorphisms have been shown to be associated with a variety of mood disorders [136, 137]. The development of selective FKBP5 antagonists might be useful to reduce the FKBP5 desensitizing effects on GRs and allow feedback inhibition of HPA axis tone.

## 12. Conclusions and expert opinion

This chapter outlines a number of different components of the HPA axis that represent attractive targets to treat mood disorders. The strongest therapeutic candidates, and the ones most directly linked to the HPA axis, are glucocorticoid receptor antagonists for depression and agonists for PTSD. It is interesting to note, that mifeprisotne (GR antagonist) and dexamethasone (a GR agonist) are presently available and FDA approved for other indications. Clinical trials with these two compounds for psychotic depression and PTSD are ongoing.

CRF1 receptor antagonists need to be more carefully evaluated in distinctive subsets of depressed patients, (ie. MDD with a history of child abuse or neglect) who exhibit chronically elevated CRF, ACTH and cortisol levels. The CRF2 receptor antagonists should

also be further studied to more elucidate their role in therapeutic treatment of mood disorders. Finally, targets that have been found by genetic and genomic screens, such as FKBP5, are potentially interesting but this field is still very much in its infancy.

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