

Targeting the Arginine Vasopressin V_{1b} Receptor System and Stress Response in Depression and Other Neuropsychiatric Disorders

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Abstract: A healthy stress response is critical for good mental and overall health and promotes neuronal growth and adaptation, but the intricately balanced biological mechanisms that facilitate a stress response can also result in predisposition to disease when that equilibrium is disrupted. The hypothalamic-pituitary-adrenal (HPA) axis neuroendocrine system plays a critical role in the body's response and adaptation to stress, and vasopressinergic regulation of the HPA axis is critical to maintaining system responsiveness during chronic stress. However, exposure to repeated or excessive physical or emotional stress or trauma can shift the body's stress response equilibrium to a "new normal" underpinned by enduring changes in HPA axis function. Exposure to early life stress due to adverse childhood experiences can also lead to lasting neurobiological changes, including in HPA axis function. HPA axis impairment in patients with depression is considered among the most reliable findings in biological psychiatry, and chronic stress has been shown to play a major role in the pathogenesis and onset of depression and other neuropsychiatric disorders. Modulating HPA axis activity, for example via targeted antagonism of the vasopressin V_{1b} receptor, is a promising approach for patients with depression and other neuropsychiatric disorders associated with HPA axis impairment. Despite favorable preclinical indications in animal models, demonstration of clinical efficacy for the treatment of depressive disorders by targeting HPA axis dysfunction has been challenging, possibly due to the heterogeneity and syndromal nature of depressive disorders. Measures of HPA axis function, such as elevated cortisol levels, may be useful biomarkers for identifying patients who may benefit from treatments that modulate HPA axis activity. Utilizing clinical biomarkers to identify subsets of patients with impaired HPA axis function who may benefit is a promising next step in fine-tuning HPA axis activity via targeted antagonism of the V_{1b} receptor.

Keywords: allostatic overload, cortisol, HPA axis, major depressive disorder, neuroendocrine

Background

A healthy response to stress is critical for good mental and overall health and promotes neuronal growth and adaptation, but the intricately balanced biological mechanisms that facilitate a stress response can also result in a predisposition to disease when the equilibrium is disrupted.¹⁻³ Allostasis is the biological process of ongoing adaptation to maintain homeostatic stability in response to challenges,^{2,3} and a key adaptive mechanism by which the body responds to stress is the hypothalamic-pituitary-adrenal (HPA) axis.⁴ The cumulative physiological impact of this adaptive response, or allostatic load, becomes allostatic overload when metabolic, hormonal, and neurotransmitter mediators of allostasis are overused or dysregulated as a result of stress, trauma, or abuse.^{2,3} It is at this point of allostatic overload and disrupted equilibrium that the cumulative impact of the body's stress response system can shift from protective to damaging, leading to diseases such as depression and other neuropsychiatric disorders (Figure 1).^{1-3,5} Research suggests that arginine vasopressin (AVP) and vasopressin receptor subtype V_{1b} play a key role in regulation of the HPA axis in response to stress, and therefore, targeting HPA axis dysregulation via modulation of the AVP-V_{1b} receptor system may offer a novel therapeutic approach to treatment of these diseases.⁶

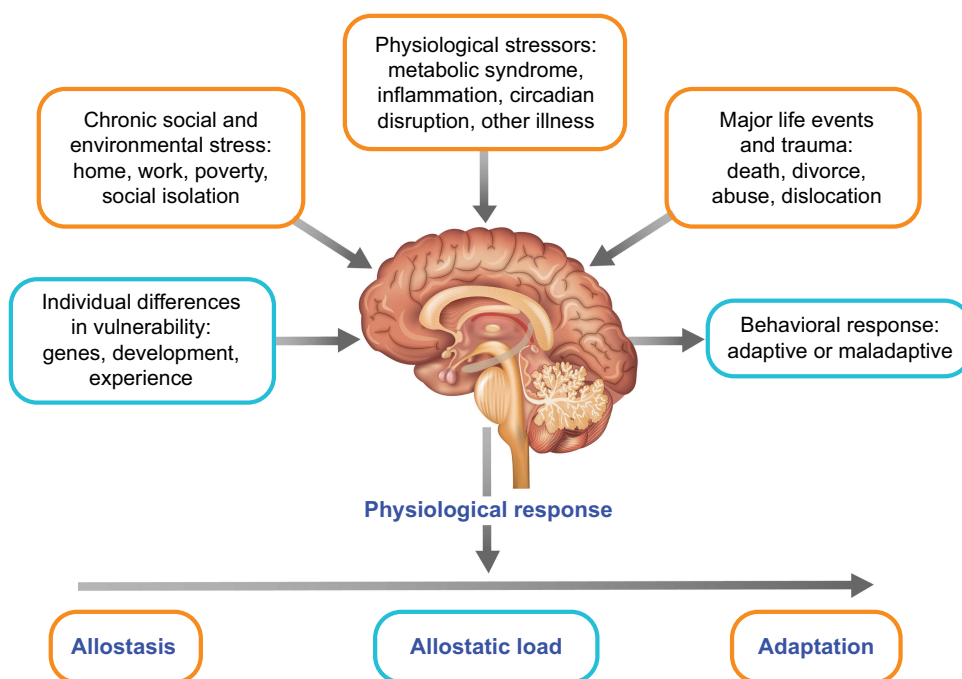


Figure 1 Allostasis and allostatic load. The brain perceives and responds to stimuli and stressors. The major function of cortisol and other mediators of allostasis is to promote adaptation. However, overuse and/or dysregulation among allostatic mediators can lead to allostatic load (or overload) and accelerate disease processes such as cardiovascular disease, diabetes, and affective disorders. Adapted from McEwen BS, Akil H. Revisiting the stress concept: implications for affective disorders. *J Neurosci.* 2020;40(1):12–21, with permission under the Creative Commons Attribution 4.0 International (CC BY 4.0) license.³

Role of the HPA Axis in Stress Response

On a neural and molecular level, the HPA axis neuroendocrine system plays a critical role in the ability of an organism to cope with and adapt to stress.^{1,2,7} Activation of the HPA axis by a physical or emotional stressor triggers a signaling cascade from the hypothalamus (Figure 2), causing neuronal synthesis and release of AVP and corticotropin-releasing hormone (CRH) into the pituitary portal circulation, where they cooperate to trigger the release of adrenocorticotropic hormone (ACTH).^{3,8} AVP alone is a weak stimulus of ACTH secretion, but, upon simultaneous release of both AVP and CRH during stress, AVP potentiates the effect of CRH to stimulate ACTH secretion.^{8,9} After its release from the pituitary, ACTH acts on the adrenal cortex to stimulate production and release of glucocorticoids (cortisol in humans; corticosterone in rodents), which serve as key allostatic mediators that penetrate the blood-brain barrier to affect brain function and behavior as well as participate in negative feedback loops to influence release of CRH and AVP from the hypothalamus and ACTH from the pituitary gland.^{1,3,7,10} However, activation of the HPA axis, including relative levels of and sensitivity to each component and temporal pattern of response, varies according to the nature of the stressor: evidence suggests that acute stress triggers a primarily CRH-mediated, dynamic, rapid, and self-limited increase in ACTH and glucocorticoids, whereas chronic (repeated) stress results in blunted and/or sustained increases in ACTH and glucocorticoids mediated by AVP.^{2,5,9,11}

Contribution of the AVP V_{1b} Receptor System to the HPA Axis Stress Response

AVP activity is mediated through 3 vasopressin receptor subtypes: V_{1a} , V_{1b} , and V_2 .¹² V_{1a} receptors are located largely in vascular smooth muscle, and V_2 receptors are located in the kidney; these receptors play key roles in vasoconstriction and fluid homeostasis, respectively, whereas V_{1b} receptors are expressed in the anterior pituitary and limbic brain regions and are involved in HPA axis regulation, stress, and emotions.^{12–15} In rats, V_{1b} receptor mRNA expression and V_{1b} receptor protein have been shown in corticotrophs, the cells in the anterior pituitary that secrete ACTH during the HPA axis stress response,^{9,13,15} as well as in the cerebral cortex, hippocampus, amygdala, and hypothalamus.^{13,15–17} The limbic system, which includes the cerebral cortex, hippocampus, amygdala, and hypothalamus, contributes to emotion, cognition, behavior, and the stress response.^{9,18} The relative contributions of limbic and pituitary V_{1b} receptors to the

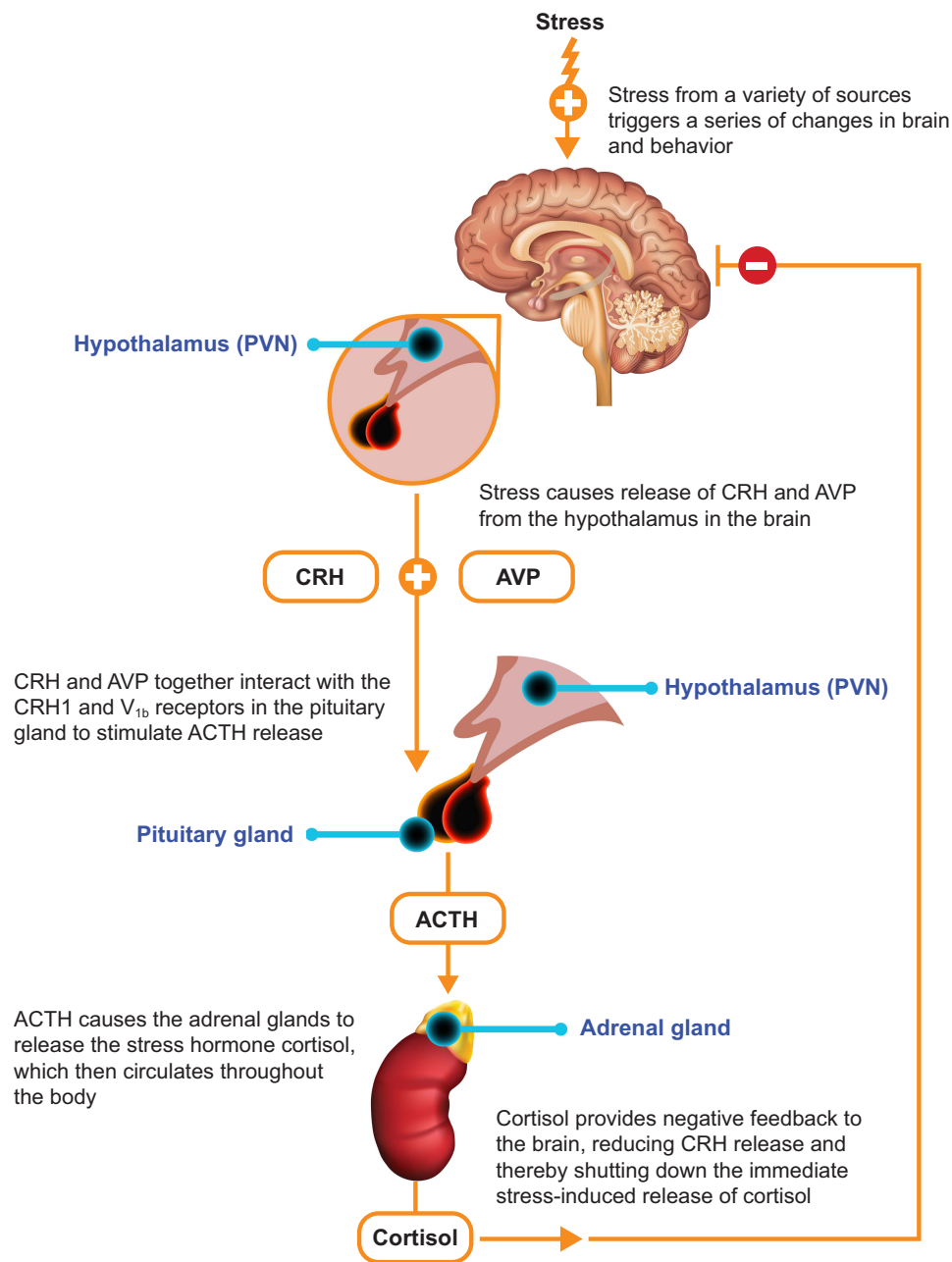


Figure 2 Key elements of the HPA axis stress response.

Abbreviations: ACTH, adrenocorticotrophic hormone; AVP, arginine vasopressin; CRH, corticotropin-releasing hormone; CRH1, CRH 1; HPA, hypothalamic-pituitary-adrenal; PVN, paraventricular nuclei; V_{1b}, vasopressin 1b.

stress response is an area of ongoing study via selective V_{1b} receptor inhibition in rodent models. Antidepressant- and/or anxiolytic-like effects can be achieved via local inhibition of V_{1b} receptors in the amygdala or the lateral septum and by systemic inhibition in hypophysectomized rats,^{19–21} confirming the limbic role of V_{1b} receptors in the stress response. Conversely, anxiolytic-like effects associated with systemic V_{1b} receptor inhibition have been prevented via hypophysectomy,²² confirming the pituitary role of V_{1b} receptors in the stress response. Thus, evidence suggests that the V_{1b} receptor modulation of the stress response occurs via both pituitary-dependent and pituitary-independent pathways.

Altered AVP and V_{1b} receptor responses to ongoing stress contribute to HPA axis dysfunction. During HPA axis homeostasis, basal CRH and AVP levels are regulated by glucocorticoid feedback inhibition as a protective mechanism to prevent inappropriate activation or overstimulation of the HPA axis in response to minor stimuli (Figure 3).⁹ During

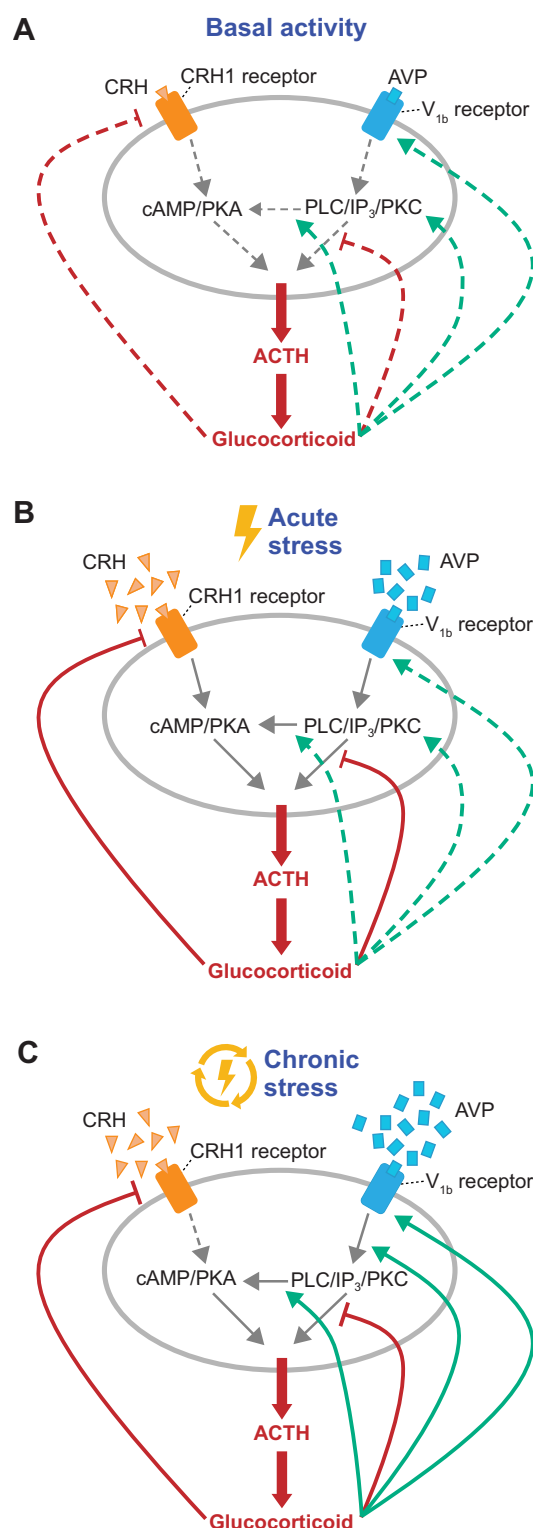


Figure 3 AVP and CRH stimulate ACTH secretion by pituitary corticotrophs. **(A)** In the basal state, the HPA axis releases glucocorticoids according to ultradian and circadian rhythms. **(B)** Activation by an acute physical or emotional stressor triggers synthesis and release of CRH and AVP from the hypothalamus to the pituitary, where they bind to the CRH1 and V_{1b} receptors, respectively, to trigger ACTH release. ACTH acts on the adrenal cortex to stimulate production and release of glucocorticoids, which serve as key allostatic mediators of brain function and behavior and regulate upstream steps via positive and negative feedback loops. **(C)** During chronic (repeated) stress, AVP is upregulated, CRH is downregulated, and AVP-mediated stimulation of ACTH release is refractory to negative glucocorticosteroid feedback due to enhanced responsiveness of PKC-mediated stimulation of ACTH release by glucocorticosteroids.

Note: Data from these studies.^{9,119,120,151,199,200}

Abbreviations: ACTH, adrenocorticotrophic hormone; AVP, arginine vasopressin; cAMP, cyclic adenosine monophosphate; CRH, corticotropin-releasing hormone; CRH1, CRH 1; HPA, hypothalamic-pituitary-adrenal; IP₃, inositol 1,4,5-trisphosphate; PKA, protein kinase A; PKC, protein kinase C; PLC, phospholipase C; V_{1b}, vasopressin 1b.

chronic stress, however, AVP becomes refractory to glucocorticoid feedback.⁹ Elevated glucocorticoid levels reduce expression of CRH and its receptor, whereas V_{1b} receptor expression and its sensitivity to AVP are enhanced, suggesting that vasopressinergic regulation of the HPA axis is critical for sustaining corticotroph responsiveness during chronic stress in the presence of high levels of circulating glucocorticoids.⁹

Stress-Related Dysregulation of the HPA Axis

During a normal stress response, activation of the HPA axis promotes a mild state of anxiety, alters attention and memory, limits dysphoria, and alters pleasure and reward processing to allow for sufficient focus on the stressor.¹ However, exposure to repeated or excessive physical or emotional stress or trauma shifts the body's stress response equilibrium, or allostatic load, to a "new normal" that is underpinned by enduring changes in HPA axis function.^{2,3} In animal models of chronic stress, changes in structure, function, and connectivity within and between the hippocampus, amygdala, and prefrontal cortex are mediated by CRH and glucocorticoids, elements of the HPA axis.^{2,23,24} Moreover, similar effects have been observed in humans in the brain regions involved in regulation of emotion and stress response (Figure 4).^{25,26} Although the relative reversibility of these stress-induced effects suggests that they are the result of a system of adaptive neuroplasticity rather than of damage, a history of stress exposure can nevertheless lead to lasting neuroplastic dysregulation of stress reactivity.^{23,26} These changes and their clinical outcomes are influenced by the type and timing of stress, the environment, and genetic and epigenetic factors^{27–38} and can manifest as hyperactive or hypoactive impairment of the HPA axis.^{27,39}

Neurobiological Changes Associated with Adverse Childhood Experiences

Exposure to early life stress (ELS) from, for example, adverse childhood experiences (ACEs) during windows of vulnerability in which the brain is still developing can lead to lasting neurobiological changes, including in HPA axis function, that significantly increase the risk of developing depression and other neuropsychiatric disorders.^{40–45} ACEs can include physical, psychological, or sexual abuse, physical or emotional neglect, or other traumatic events during childhood³⁹ and are an important risk factor for many neuropsychiatric disorders, including depression.^{41,42} In a meta-analysis of more than 17,000 adults with depression, nearly half (46%) reported a history of childhood maltreatment, with an estimated prevalence of 43% for childhood emotional neglect, 37% for childhood emotional abuse, 36% for childhood physical neglect, 28% for childhood physical abuse, and 25% for childhood sexual abuse.⁴³ Furthermore, patients with major depressive disorder (MDD) were almost 4 times more likely than healthy controls to have been mistreated as children, and those with persistent depressive disorder were almost 9 times more

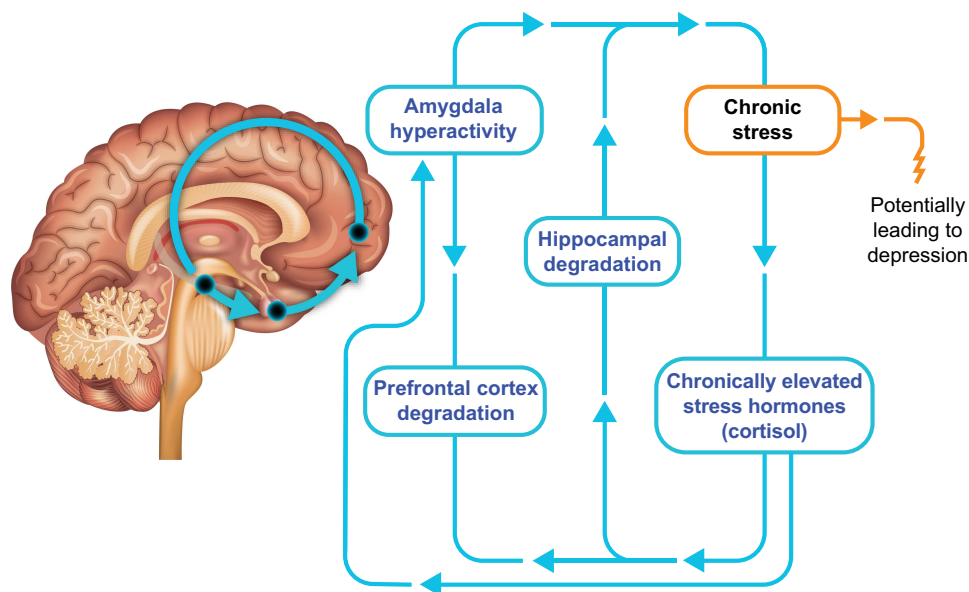


Figure 4 Stress responses in the brain. In response to chronic stress, long-term effects of elevated circulating levels of cortisol include structural and connectivity changes in the brain and activation of the brain's fear center in the amygdala. These changes can result in worsening stress and contribute to the development of depression.

likely than healthy controls to have experienced multiple forms of abuse or neglect.⁴⁴ Approximately 60% of adults with depression have experienced ≥ 1 ACE,^{44,45} and ELS is 4 times more prevalent in patients with depression than in healthy controls⁴⁵ and is associated with earlier onset of depression,^{43,45} reduced response to depression treatment,^{43,45} and reduced life expectancy.^{42,46–49}

During the heightened neuroplasticity of childhood, ELS or ACE exposure is also associated with substantial effects on brain structure, function, connectivity, and network architecture, including brain regions involved in regulation of emotion and stress response.^{25,50,51} Preclinical and clinical research have shown an association between ACEs and lasting changes to HPA axis function, which may contribute to the risk and course of depression.^{38,42,43,45} The nature of HPA axis impairment (eg, hyperactivity or hypoactivity) following an ACE is influenced by the type of ACE, psychosocial support, and genetic and epigenetic factors.^{38,52} Consequently, depression in patients with a history of ELS may be a distinct biologic endophenotype, with a unique clinical feature, course of illness, and response to therapy.^{31,38}

HPA Axis Impairment in Depression, Neuropsychiatric Disorders, and Beyond

HPA axis impairment in patients with depression is considered among the most reliable findings in biological psychiatry.¹⁰ Alterations in activity of limbic regions that are regulated by the HPA axis may contribute to heightened anxiety, changes in attention and memory, dysphoria, and altered pleasure and reward processing.¹ Stress has been shown to play a major role in the pathogenesis and onset of depression and to contribute to increased vulnerability to developing depressive symptoms.^{53,54} Polymorphisms in genes involved in HPA axis functioning have been shown to influence stress response, risk of depression,^{55–58} and response to antidepressant treatment,^{56,59} and several mechanisms of HPA axis impairment have been implicated in the pathogenesis of depression, including cortisol resistance, reduction in neurogenesis, increase in cytokines, and immune system activation.^{10,60} Significant HPA axis hyperactivity, as indicated by elevated serum, urinary, salivary, cerebral spinal fluid, and hair cortisol levels, occurs more often in patients with depression than in healthy controls,^{61,62} with nearly three-quarters of people with depression demonstrating elevated cortisol levels.⁶¹ Furthermore, elevated cortisol may be one of the few prospective predictors of MDD onset and relapse or recurrence⁶³ and may correlate with the severity of depressive symptoms.⁶¹ For example, recent dramatic increases in stress and depressive symptoms associated with the COVID-19 pandemic and lockdown have been correlated with changes in cortisol levels,^{62,64,65} and elevated pre-pandemic cortisol levels were predictive of depressive symptoms during the pandemic (Box 1).⁶²

Box 1 Effects of the COVID-19 Pandemic on Global Mental Health

- COVID-19–related stress is associated with depressive symptoms,^{189–193} and individuals with higher levels of COVID-19–related stress are more likely to screen positive for depression or major depressive disorder.^{192,194,195}
- Exposure to a higher number of COVID-19–related stressors is associated with a greater risk of depression.^{191,192}
- Globally, rates of depressive symptoms increased 2- to 10-fold during the COVID-19 pandemic, with pre-COVID prevalence rates of 1.3–11.5% that increased to 18.3–33.7% in the peri-COVID era.^{128–140}
- US rates of depressive symptoms increased from 6.5–8.9%^{139,196} in the years shortly before the COVID-19 pandemic to 14.2–27.8% early in the pandemic^{139,191} and have remained elevated (25.0% as of October 5–17, 2022).¹³⁹
- In nationwide surveys of US adults, the prevalence of moderate-to-severe depression increased through the COVID-19 era and reached rates ≥ 3 times higher than those of the pre-COVID era.^{193,197}
- Changes in biomarkers of hypothalamic-pituitary-adrenal axis function have been observed during vs before the COVID-19 pandemic and lockdown and may be related to perceived stress and depressive symptoms.^{62,64,65}
- Serum cortisol concentrations significantly increased in women and decreased in men during vs before the COVID-19 lockdown.⁶⁵
 - Significant increases in serum cortisol concentrations were observed in patients who experienced moderate-to-high stress.⁶⁵
 - Changes in serum cortisol concentrations were significantly associated with both perceived stress and depression.⁶⁵
- Hair cortisol concentrations (HCCs) may serve as a marker of psychological susceptibility to stress, as elevated pre-pandemic HCCs among adults aged ≥ 50 years significantly predicted depressive symptoms during COVID-19;⁶² however:
 - Both abnormally high and abnormally low HCCs were reported in healthcare workers during the COVID-19 pandemic.⁶⁴
 - Both increases and decreases in HCC were reported before vs during the COVID-19 lockdown.¹⁹⁸

Profound changes in HPA axis function during pregnancy and in the perinatal period may also contribute to postpartum depression.⁶⁶ Under healthy conditions, significantly increased HPA axis activity is observed in the third trimester, followed by a decline in activity after the birth.^{67,68} Cortisol concentrations rise during pregnancy due in large part to placental CRH production, which stimulates production of and is subject to positive feedback by maternal and fetal cortisol.⁶⁹ During and after birth, the HPA axis is subject to abrupt changes when the placental contribution of CRH ceases and cortisol concentrations decrease substantially during the postpartum period.⁶⁹ Among women who develop perinatal or postpartum depression, elevated cortisol levels observed in some studies suggest that the HPA axis may not be adequately suppressed after birth.^{70–72} Compounding the effects of fluctuating cortisol, changes in estrogen during pregnancy may also alter HPA axis activity. In rats, estrogen induces remodeling of the CA1 region of the hippocampus, an area involved in suppression of the HPA axis stress response; in humans, estrogen alters HPA axis activity by increasing basal cortisol levels and blunting cortisol suppression by dexamethasone, similar to alterations observed in depression.^{24,73} Combined, these dramatic changes in hormone activity during and after pregnancy may impose a dysregulating effect on the HPA axis and result in postpartum depression.⁶⁶ Likewise, MDD rates have been shown to increase 2- to 3-fold during the menopause transition, and research has suggested that hormonal changes leading to HPA axis impairment in cortisol reactivity may increase vulnerability to stress and depression in this population.⁷⁴

Changes in HPA axis function have been implicated in a number of other neuropsychiatric conditions, as well. Reduced HPA axis activity appears to contribute to posttraumatic stress disorder (PTSD).^{75,76} While higher cortisol in children is predictive of PTSD, enhanced negative feedback inhibition of the HPA axis is observed in individuals experiencing PTSD, indicated by simultaneously reduced circulating cortisol and increased CRH coupled with enhanced cortisol suppression in response to dexamethasone challenge.^{76,77} In contrast, anxiety disorders are associated with hypercortisolemia and reduced feedback inhibition of the HPA axis.^{54,78} An increased susceptibility to anxiety due to ELS may be a consequence of HPA axis hyperactivity in the form of an imbalance between glucocorticoid receptor- and mineralocorticoid receptor-mediated negative feedback.⁷⁸ Excessive HPA axis activity is also a feature of bipolar disorder,⁷⁹ with more robust hyperactivity observed in patients with severe manic symptoms⁸⁰ or a history of suicidal behavior.⁸¹ In schizophrenia, changes in hair cortisol concentration are negatively associated with delusion severity, and evidence supports the use of measures of HPA axis activity as biomarkers for associated brain tissue loss.^{82,83} A dysregulated HPA axis response to stress is associated with anorexia and bulimia nervosa and is exacerbated by the added experience of childhood trauma.^{84–86} Attenuated HPA axis activity persisted following treatment for anorexia or bulimia and therefore may represent a risk factor for an eating disorder rather than a consequence thereof.⁸⁶

One contributor to HPA axis impairment in patients living with these disorders is dysregulation of the AVP V_{1b} receptor system, specifically.^{61,87,88} Elevated AVP levels have been shown in patients with depression,^{89–93} including anxious-retarded depression⁸⁹ and melancholic-type depression,⁹⁰ as well as in patients with bipolar disorder,^{91,93} obsessive compulsive disorder,⁹⁴ bulimia nervosa,⁸⁵ and PTSD,⁹⁵ indicating overactivation of AVP in these patient populations.⁶ Involvement of the AVP- V_{1b} receptor system HPA axis dysregulation in patients with depression is further supported by positive correlations demonstrated between AVP and cortisol levels,^{89,96} particularly among those who have attempted suicide.⁹⁶ These data provide support for increased sensitivity of the V_{1b} receptor to AVP regulation of the HPA axis stress response in the presence of elevated cortisol in patients with depression.^{88,97}

The central role of the HPA axis in allostasis, allostatic load, and allostatic overload suggests broader implications beyond neuroplasticity for HPA axis dysfunction.^{4,98} Because the HPA axis neuroendocrine system dynamically influences a wide variety of physiological processes, changes in its function are associated with a broad range of long-term health consequences.^{3,61,99,100} Among patients with depression, HPA axis dysregulation as demonstrated by elevated cortisol levels is associated with increased risk of other medical conditions in which HPA axis dysregulation has been implicated, including diabetes, obesity, metabolic syndrome, cardiovascular disease, cognitive dysfunction, and osteoporosis.^{61,99–111} Overall, evidence suggests that HPA axis dysfunction underpins a bidirectional relationship between many of these comorbidities and depression.^{110,112–114}

Cortisol as a Biomarker of HPA Axis Dysfunction

Depression is a clinically heterogeneous condition comprising several subtypes that may be characterized by unique HPA axis profiles that range from hyperactivity to hypoactivity,⁶⁸ but patients whose depression is associated with HPA axis impairment may benefit from treatment that selectively modulates a single target within the HPA axis.⁶ For example, melancholic depression (characterized by anhedonia, insomnia, loss of appetite, feelings of worthlessness, and diurnal mood variability) and psychotic depression (characterized by delusions or hallucinations) are associated with HPA axis impairment as demonstrated by elevated cortisol levels.^{61,115,116} Similarly, patients who are hospitalized for depression and older patients with depression are more likely than nonhospitalized patients and younger patients, respectively, to have HPA axis impairment as demonstrated by elevated cortisol levels.⁶¹

Conversely, some studies have shown a reduction in basal cortisol levels in depression and other neuropsychiatric disorders, indicating HPA axis hypoactivity, rather than hyperactivity, in some patients.^{61,68,77,117} For example, studies have suggested that patients with atypical depression (characterized by hypersomnia, fatigue, hyperphagia, weight gain, and emotional reactivity) may have lower cortisol levels than those with nonatypical depression and may not differ from healthy, nondepressed individuals.^{61,115} Furthermore, among patients exposed to chronic stressors, including patients with PTSD with or without MDD, reduced cortisol levels were directly proportional to the length of elapsed time between precipitating traumatic event and cortisol assessment.^{77,117,118} These observations suggest that, following exposure to chronic stress, HPA axis dysregulation follows a nonlinear course in which cortisol levels rise initially in response to the traumatic event or in anticipation of events, then taper over time with increasing chronicity until a state of hypocortisolism is reached.

Also important when considering the relationship between cortisol and depression are the diurnal (circadian) and ultradian (pulsatile) rhythms by which cortisol is released under basal conditions. Ultradian oscillations are characterized by pulsatile bursts of cortisol, CRH, AVP, and ACTH secretions.^{119,120} Mathematical modeling, confirmed in vivo in rats, supports the hypothesis that the ultradian pulses exchanged within the pituitary-adrenal system provide a dynamic feedforward-feedback regulation that can function independently of hypothalamic control.^{120,121} Ultradian rhythms contribute to the responsiveness of the HPA axis to stress, and changes in ultradian pulse amplitude and frequency are the foundation of circadian rhythm.¹¹⁹

In healthy individuals, the diurnal pattern is characterized by a marked rise in cortisol upon waking that peaks 50–100% higher than baseline 30–45 minutes later and returns to baseline approximately 1 hour after waking.¹²² Any point of the diurnal rhythm may be affected in depression, and the specific nature of cortisol changes can be related to disease severity or subtype.^{122,123} For example, flattened diurnal cortisol rhythms have been observed in severe depression, and distinguishable patterns have been identified in depressed patients with comorbid anxiety.^{124,125} Both higher and lower/blunted cortisol waking responses have been observed in depression, with the former exhibiting a predictive relationship with major depressive episodes.^{122,126,127} Together, data from cortisol studies suggest that HPA axis impairment can result from either too much or too little cortisol, and HPA axis response and disease characteristics may depend on a variety of moderating influences such as features of the stressor, the person, and timing. As a measure of HPA axis function, therefore, cortisol may be a useful biomarker for identifying distinct types of patients with depression who may benefit from treatments that modulate HPA axis activity.⁶⁸

Treating Depression and Other Neuropsychiatric Disorders by Targeted HPA Axis Modulation

In the approximately 4 years since the onset of the COVID-19 pandemic, global prevalence rates of depressive symptoms have increased from 1.3–11.5% to 18.3–33.7%.^{128–140} However, because only one-third of patients with depression achieve remission with their first antidepressant and a further third of patients fail to achieve remission with any antidepressant and will be considered treatment resistant, a significant unmet need still remains for new treatment approaches with novel mechanisms of action.^{141–144} To this end, modulating HPA axis activity with targeted treatments may be a promising approach for patients with depression and other neuropsychiatric disorders associated with HPA axis

impairment.^{109,145} A meta-analysis of 16 randomized clinical trials and 7 open-label studies evaluating HPA axis-targeted therapies reported significant clinical benefits compared with controls, underscoring the potential of this approach for treating patients with depression.¹⁴⁵ Also, some individual historical clinical trials of HPA axis-targeted therapies did not show clinical benefits in the overall study population, although post hoc subanalyses of these trials have shown benefit in some patient subgroups with HPA axis hyperactivity.^{75,146,147} Historically, failure of individual clinical trials to demonstrate efficacy of HPA axis-targeted therapies in patients with depression and other neuropsychiatric disorders may reflect the heterogeneity of the disorders and the broad patient populations enrolled.^{6,109,147,148} However, careful selection of patients with biomarkers reflecting HPA axis impairment, such as elevated cortisol levels, may be helpful in identifying which patients would benefit most from HPA axis-targeted treatment approaches.^{6,147}

Research is ongoing to identify promising therapeutic targets within the HPA axis.^{149–151} Studies of CRH receptor antagonists have not reported significant improvements in depression, and the effects of glucocorticoid receptors in the treatment of depression are inconsistent.^{6,75,152} On the other hand, targeted antagonism of the V_{1b} receptor is a promising treatment approach in patients with depression.^{6,146} In animal models, antagonism of the V_{1b} receptor has been shown to attenuate depressive-like and anxiety-like behaviors, particularly in stressful situations.^{6,153} For example, the Brattleboro rat strain, which is characterized by a spontaneous AVP deficiency caused by a single nucleotide deletion in the AVP gene, exhibits reduced depressive-like and anxiety-like behaviors.^{153,154} Moreover, among Wistar rats that have been selectively bred for high anxiety-like behavior (HAB) or low anxiety-like behavior (LAB), the HAB lines exhibit higher AVP expression in the paraventricular nuclei of the hypothalamus than the LAB lines.¹⁵⁵ In male HAB rats, dexamethasone suppression of the diurnal increase in circulating ACTH levels was significantly less efficient and subsequent CRH-stimulated plasma ACTH and corticosterone responses were significantly higher than in male LAB rats; pretreatment with a selective $V_{1a/b}$ receptor antagonist abolished the CRH-stimulated response in dexamethasone-pretreated male HAB rats, demonstrating that vasopressinergic activation accounts for the disrupted HPA axis response in male HAB rats.¹⁵⁵ Additional animal model studies have shown that antagonism of the V_{1b} receptor attenuates depressive-like and anxiety-like behaviors.^{6,19–22,146,153,156–171} Consistent effects of V_{1b} receptor antagonism were not observed in 2 studies; although the reason for this discrepancy is unknown, the researchers speculated that methodological differences in the behavior assays used may have been a contributing factor.^{6,161,167}

In humans, the V_{1b} receptor antagonist ABT-436 has demonstrated reduction of HPA axis parameters such as plasma ACTH, serum and urine cortisol, and urine total glucocorticoids in healthy adults.¹⁷² In patients with MDD, research has suggested that ABT-436 was associated with reduced levels of plasma ACTH and cortisol, suggesting potential attenuation of HPA axis activity; further, this study showed statistically significant improvements with ABT-436 over placebo on 2 of the 5 Mood and Anxiety Symptom Questionnaire (MASQ) subscales (ie, subscales “General Distress-Depressive Symptoms” and “General Distress-Mixed Symptoms”) but not in Hamilton Depression Rating Scale [HDRS]) scores following 1 week of treatment.¹⁷³ The V_{1b} receptor antagonist SSR149415 failed to clearly demonstrate effective treatment of symptoms in patients with generalized anxiety disorder or MDD, although doses used in these trials may have been insufficient to block HPA axis activity and achieve therapeutic effects; these failures may also reflect the heterogeneity of the illness or the broad patient populations enrolled.^{6,61,174} Using doses determined based on V_{1b} receptor occupancy and nonclinical behavioral models,^{175,176} adjunctive treatment with the V_{1b} receptor antagonist TS-121 reduced depressive symptoms as assessed by the Montgomery-Åsberg Depression Rating Scale (MADRS), Clinical Global Impression of Severity (CGI-S), and Strengths and Difficulties Questionnaire (SDQ) measures in patients with MDD and inadequate response to their current antidepressant, although the number of patients analyzed was small and these reductions were not statistically significantly different from placebo.¹⁴⁶ However, post hoc analyses showed that adjunctive treatment with TS-121 was associated with greater separation in efficacy outcomes compared with placebo among patients with MDD and higher cortisol levels consistent with elevated HPA axis activity.^{6,146} These observations suggest that, within the subset of patients with MDD who had been screened and met trial inclusion criteria, V_{1b} receptor antagonists may be more efficacious in patients with elevated cortisol levels, consistent with HPA axis hyperactivity, relative to an unscreened population of patients with MDD. Based on these ANC-501 (formerly TS-121) findings and favorable ANC-501 safety and tolerability, a phase 2 trial of adjunctive ANC-501 (NCT05439603) is currently in progress in adults with MDD with history of inadequate response to standard antidepressants and disrupted HPA

axis function as indicated by elevated cortisol levels.^{146,177,178} Based on the results from the phase 2 trial, a double-blind, placebo-controlled trial of ANC-501 is planned for 2023 in patients with depression.¹⁷⁹

Although HPA axis dysfunction has been consistently demonstrated in patients with depression and other neuropsychiatric disorders, specific aspects of this dysfunction (eg, hyper- vs hypofunction) have differed across studies, which may be due to the unique pathological characteristics of different neuropsychiatric diseases and the heterogeneity and syndromal nature of many illnesses, as well as the methods employed to study them.^{61,180,181} Regarding V_{1b} receptors specifically, their activity and the potential efficacy of antagonists in treating neuropsychiatric disorders may also depend upon contextual effects. In rats exposed to acute stress, V_{1b} antagonism reduced ACTH response following lipopolysaccharide injection and restraint stress, but not noise stress.¹⁸² In addition, glucocorticoids are subject to regulation by both pituitary-dependent and -independent regulation of the adrenal gland: in a rat chronic stress model, increases in basal corticosterone levels and enhanced rapid corticosterone secretion following exposure to acute stress were both unaffected by CRH antagonism but were sensitive to sympathetic ganglion blockade.¹⁸³ These findings suggest a role for the sympathetic nervous system in regulating stress-induced glucocorticoid levels.¹⁸³ In those patients enrolled in the MDD trial of ANC-501 described above, the potential association of ANC-501 efficacy with the clinical biomarker of elevated cortisol may suggest that HPA axis-targeted therapies may only be able to demonstrate clinical treatment effects in patients with measurable HPA axis dysfunction.¹⁴⁶ Thus, seemingly inconsistent findings across studies may indicate differences in the nature of HPA axis disturbances specific to the illness under investigation, the study design, or the influence of other contextual factors. Under those circumstances, differing results observed across clinical trials may be more indicative of inherent heterogeneity and the need to accurately identify appropriate testing conditions and more specific patient subgroups than of irregularities in V_{1b} antagonist effects.

Unmet Need in Global Mental Health

In 2019, depressive disorders were among the 10 leading noninfectious drivers of increasing global disease burden.¹⁸⁴ In 2020, the estimated global prevalence of MDD (unadjusted) was 193 million people, but many determinants of poor mental health outcomes were exacerbated that year by the emergence of the COVID-19 pandemic, increasing the resulting global MDD prevalence (adjusted) by 28% to 246 million people (Box 1).¹⁸⁵ Among patients with depression who receive treatment, research has suggested that up to one-third do not achieve remission of symptoms, even after attempting up to 4 different sequential lines of therapy.¹⁸⁶ Therefore, significant unmet needs remain not only for treatment of the global burden of depressive disorders, but also for new treatment approaches with novel mechanisms of action for patients with depression and other neuropsychiatric disorders.

Conclusions

Despite early favorable indications in animal models for targeting HPA axis dysfunction for the treatment of depressive disorders, translation of these findings into clinical efficacy has been challenging,^{6,23,148} particularly given the heterogeneity and syndromal nature of these diseases.^{3,187} Therefore, confronting this heterogeneity³ by utilizing an appropriate clinical biomarker,¹⁸⁸ such as elevated cortisol, to identify the subset of patients with impaired HPA axis function is a promising next step in modulating HPA axis activity via targeted antagonism of the V_{1b} receptor, facilitating a more tailored approach to the treatment of depression and other neuropsychiatric disorders.

Abbreviations

ACE, adverse childhood experience; ACTH, adrenocorticotrophic hormone; AVP, arginine vasopressin; CGI-S, Clinical Global Impression of Severity; CRH, corticotropin-releasing hormone; ELS, early life stress; HAB, high anxiety-like behavior; HCC, hair cortisol concentration; HDRS, Hamilton Depression Rating Scale; HPA, hypothalamic-pituitary-adrenal; LAB, low anxiety-like behavior; MADRS, Montgomery-Åsberg Depression Rating Scale; MASQ, Mood and Anxiety Symptom Questionnaire; MDD, major depressive disorder; PTSD, post-traumatic stress disorder; SDQ, Strengths and Difficulties Questionnaire; V_{1a} , V_{1b} , and V_2 , vasopressin 1a, 1b, and 2 receptors.

Data Sharing Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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Author Contributions

All authors made substantial contributions to conception, design, and scope of this review article; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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Disclosure

S.J.K. and L.D. are employees of and P.P. is a consultant for EmbarkNeuro, Inc. In addition, S.J.K. has a patent “METHODS OF TREATING DEPRESSION WITH 1,2,4-TRIAZOLONE DERIVATIVES” pending to EmbarkNeuro. The authors report no other conflicts of interest in this work.

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