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Hypothalamic-Pituitary-Adrenal Axis

Elevated cortisol levels and hypothalamic-pituitary-adrenal (HPA) hyperactivity are found in depressed individuals at a higher rate than in the general population. Cortisol hyperactivity in depression was first identified in the 1950s and 1960s. Research over the last half century has provided much specific information with regard to the HPA abnormalities in depression. However, knowledge pinpointing the primary cause or locus of HPA alterations in depression remains elusive. Recent research identifies alterations in the glucocorticoid receptor (GR; one the two types of receptors for cortisol). However, the ultimate causes of HPA dysregulation and GR alterations in depression are likely to be multifaceted. Presented here is a brief review of HPA axis function and recent findings on HPA alterations in depression.

Overview of HPA Axis Physiology and Cortisol Negative Feedback

Secretion of glucocorticoids from the adrenal gland is under the control of several upstream hormonal regulators, namely, corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP), released from the hypothalamus, and adrenocorticotropin hormone (ACTH), released from the pituitary gland. Cortisol is the primary endogenous glucocorticoid in primates, and corticosterone is primary in rodents. Variation in glucocorticoid levels occurs as a function of many factors, including circadian variation (glucocorticoids are high in the morning and low in the evening), and in response to food intake, physical activity, and psychological stress (e.g., psychosocial threat).

One of cortisol's most important functions is in shutting down or "containing" a stress response. For instance, cortisol plays a negative feedback role in reducing its own further release. In other words, when cortisol is released into the blood stream from the adrenal gland, the elevated blood levels of cortisol impinge upon the pituitary gland and the brain, causing a reduction in HPA-axis activity, and thus a reduction in cortisol secretion. In addition, cortisol elevations regulate sympathetic nervous system and immune activation (e.g., inflammation) during recovery from a stress response.

Cortisol is considered a stress hormone because adrenal production and secretion of cortisol occur during situations that are considered stressful. *Stress* is alternatively conceived as a pathophysiological process related to real or perceived inability to cope with environmental demands, or as an adaptation to environmental demands that promotes homeostasis. Research has associated cortisol with stress-related disease and pathology, and in popular culture, cortisol elevations are commonly thought of as harmful. Indeed, chronic cortisol elevations due to a failure to adequately regulate the HPA axis

can eventually damage target tissues. However, cortisol is a life-sustaining hormone and has many essential functions that allow coping and adaptation to stressors. For instance, cortisol plays a role in metabolism by increasing availability of energy stores. Equally important are cortisol's effects on psychological functioning. Acute elevations facilitate memory formation. Chronic elevations impair many cognitive processes. The effects of glucocorticoids on many target tissues and behavioral processes follow an inverted U-shaped function in which moderate elevation of cortisol enhances functioning, while extreme or prolonged glucocorticoid elevation impairs functioning. Thus, the problem occurs when cortisol fails to restrain aspects of a stress response, including failure to contain its own activity through negative feedback.

The Nature of Glucocorticoid Alterations in Depression

Most depressed individuals are not hypercortisolemic on a daily basis. However, when examined longitudinally, depressed individuals are more likely to show elevated cortisol levels (especially in the evening) than healthy individuals. Research has established the existence of an enhanced CRH drive, and a related cortisol negative feedback deficit in a subset of individuals with major depressive disorder. In other words, research has shown both enhancement of excitatory control as well as reduced negative feedback inhibition of the HPA.

The dexamethasone suppression test (DST) was the first test used to study the negative feedback effects of cortisol. Dexamethaone (DEX) is a synthetic glucocorticoid that, acting as a negative feedback signal, suppresses ACTH secretion and thus suppresses cortisol release. The classic DST entails administration of DEX at 11:00 p.m. and measurement of cortisol levels the next day at one or more time points. Depressed individuals show an escape from the suppressive effects of DEX (i.e., fail to show suppressed cortisol levels on the day following DEX administration) at a higher rate than healthy controls.

However, the DST is a crude measure of HPA negative feedback with low sensitivity, detecting only 20% to 30% of depressed individuals (Holsboer, 2001). More sophisticated assessments have confirmed the existence of the negative feedback deficit in a larger percentage of patients with major depressive disorder. For instance, Holsboer and colleagues developed the combined DEX-CRH test, in which they measured ACTH response to CRH infusion in patients pretreated with DEX (Holsboer, 2001). On this test, pretreatment with DEX fails to restrain ACTH response to CRH administration in up to 80% of depressed patients. This test provides further evidence for a negative feedback deficit in depression (Holsboer, 2001).

HPA alteration is most prevalent in depressed individuals who have a history of childhood trauma (Heim & Nemeroff, 2001), are older, or show severe symptoms. In addition, research conducted by Schatzberg and colleagues (Belanoff, Kalehzan, Sund, Fleming Ficek, & Schatzberg, 2001) suggests that cortisol elevation is more likely to occur in depressed individuals who are psychotic, and is hypothesized to be causally related to psychotic symptoms in psychotic depression. It is also important to note that hypocortisolism (i.e., low cortisol) is sometimes found in depression, particularly in atypical depressives (Murck, 2003). The mapping between HPA alteration and depressive subtype is far from one-to-one. HPA alteration has also been found in other forms of psychopathology and stress-related pathology, including schizophrenia and posttraumatic stress disorder.

Glucocorticoid Signaling in the Brain

Cortisol crosses the blood-brain barrier and modulates activity in brain structures primarily via two types of corticosteroid receptors: mineralocorticoid receptors (MRs) and glucocorticoid receptors (GRs). Negative feedback regulation of the HPA axis is mediated both by MRs and GRs. GRs have low affinity for cortisol and are occupied only when circulating cortisol levels are high.

Therefore, the role of GRs in inhibition of the HPA axis is specific to times when circulating glucocorticoids are high. Conversely, because of MRs' high affinity for glucocorticoids, MRs are occupied when circulating levels of cortisol are low. Thus, MRs are important in tonic inhibition of the HPA axis.

Various investigators have hypothesized that a corticosteroid receptor deficit underlies the negative feedback deficit observed in major depressive disorder. A GR deficit has long been hypothesized to underlie the HPA negative feedback deficit in depression (Sapolsky & Plotsky, 1990). Such a GR deficit would cause inefficient return to baseline cortisol elevation following the cessation of a stressor (i.e., to use the above analogy: "faulty breaks"). An accumulation of research provides circumstantial evidence for such a GR deficit. For instance, peripheral immune cell activity is not as sensitive to the immunosuppressive effects of glucocorticoids (which are mediated by GRs) in depressed compared to healthy individuals (Pariante & Miller, 2001, for review). In fact, individuals who show escape from the suppressive effects of DEX exhibit less GR-mediated inhibition of immune activity by glucocorticoids. Furthermore, antidepressants increase GR function through a variety of mechanisms, which is associated with enhancement of HPA feedback inhibition in animals (Holsboer & Barden, 1996; Pariante, Thomas, Lovestone, Makoff, & Kerwin, 2004).

Consequently, several investigators have hypothesized that "insufficient glucocorticoid signaling" (i.e., insensitivity of target tissues to the effects of glucocorticoids) is an important aspect of major depressive disorder (Holsboer, 2001; Pariante et al., 2004). It is important to note that numerous pathways could account for reduced capacity of glucocorticoids to modulate activity in target tissues. In addition to reduced number or sensitivity of corticosteroid receptors, insufficient glucocorticoid elevation (i.e., hypocortisolism) or reduced access of glucocorticoid to its receptor (i.e., reduced bioavailability of cortisol) may also play a role in insufficient glucocorticoid signaling (Pariante et al., 2004). As mentioned above, hypocortisolism has at times been found in depression (Murck, 2003). In addition, new evidence suggests that alterations in the blood-brain barrier reduce the bioavailability of cortisol (Pariante et al., 2004). Cortisol's access to the brain is limited by steroid transporters at the blood-brain barrier that regulate intracellular concentration of glucocorticoids by expelling the hormone back into the plasma. Variation in steroid transporter functioning has been shown to modulate activity of the HPA axis. Thus, even within the context of cortisol excess in the periphery, overactivation of steroid transporters could cause inadequate access of cortisol to the brain. This mechanism may have importance for depression. Antidepressant medications regulate cellular levels of cortisol by inhibiting steroid transporters (Pariante et al., 2004). In summary, several mechanisms in addition to reduced sensitivity or number of GRs could account for altered glucocorticoid signaling in the brain in depression.

The ramifications of data regarding glucocorticoid signaling are currently unknown. It may be the case that cortisol elevation in the periphery bathes the brain in too much cortisol, causing a "vicious cycle" with downregulation of GRs, which causes negative feedback deficits, further cortisol elevation, further downregulation of GRs and so on. This scenario is at times observed during chronic stress in animals and has been described with the glucocorticoid cascade hypothesis (Sapolsky, Krey, & McEwen, 1986). Another possible scenario entails reduced bioavailability of cortisol and reduced access of cortisol to the brain. This situation would entail elevated cortisol in the periphery paired with too little cortisol or ineffective activity of cortisol in the brain. Thus, it is currently unknown whether depression entails too much or too little cortisol "bathing" the brain. Either way, evidence suggests that insufficient glucocorticoid signaling in the brain (due either to GR downregulation or other factors) is an important aspect of depression. In sum, alterations in glucocorticoid signaling at GRs are hypothesized to underlie HPA negative feedback deficits observed in depression. Consistent with

these findings, pharmacological treatments that target GRs have shown some success in the treatment of depressive symptoms. Various research groups are investigating the use of drugs that alter corticosteroid signaling as an adjunct to traditional antidepressant medication (e.g., Belanoff et al., 2002).

It should also be noted that in addition to negative feedback pathways, positive feedback loops exist through the amygdala and other brain regions, in which cortisol elevations serve to increase brain CRH and HPA activation. Thus, not all glucocorticoid effects on the brain dampen HPA activity. Positive and negative feedback circuitry operate in parallel. In addition to the deficits in HPA negative feedback described above, evidence suggests that positive feedback loops in depression may be overactive (Reul & Holsboer, 2002). Thus, positive feedback loops through the amygdala and other brain regions, which mediate enhancement of brain CRH by peripheral cortisol elevations, are hypothesized to play a role in the etiology of depression.

Lifelong Alterations in GR Gene Expression

HPA dysregulation in depression is primarily state dependent. However, it is unknown whether the hypothesized deficits in glucocorticoid signaling are state dependent or represent lifelong individual differences. Research in animals has established the existence of lifelong individual differences in GR functioning in the brain, which are a result of either inherited species differences or early environmental manipulation (Meaney et al., 1996). In rodents, early life experiences, such as maternal separation and "handling," cause lifelong effects on HPA regulation and GR function. Maternally separated rodents are taken from their mothers daily for relatively long intervals (e.g., 3 hours a day). Handling is a manipulation in which young rodents are taken away from their mothers for a short time (approximately 15 minutes a day). When compared to control rodent pups, these manipulations cause changes in stress sensitivity and HPA-axis regulation that last through adulthood. Maternal separation causes elevated corticosteroid responses to stress and reduced tone in HPA negative feedback functioning, whereas handling has the opposite effects on HPA responses, causing salubrious effects which last into the rodents' adult life.

Michael Meaney and colleagues have performed a series of elegant studies, which have shown that the effects of handling are mediated by lifelong effects on GR gene expression (Weaver, Diorio, Seckl, Szyf, & Meaney, 2004). They have found that handled rat pups receive more attention (i.e., licking and grooming) from their mothers. This enhanced maternal care in early life permanently alters the development of GR gene expression in the hippocampus and causes reduced HPA responses to acute or chronic stress. While these early environmental conditions do not alter the DNA sequence itself, they cause epigenetic changes in the expression of transcription factors that drive GR expression. These data provide a very important example in mammals of how early life experiences can cause changes in gene expression that alter stress sensitivity into adulthood. As described above, GR functioning appears to have important ramifications for HPA dysregulation in depression. It is thus very compelling that maternal separation and handling have opposite lifelong effects on GR functioning. This animal model provides an important demonstration of how early life experiences may cause lifelong biological changes that act as a diathesis for depression.

Conclusions

Presented herein is a biologically oriented perspective arguing that alterations in GR and cortisol signaling in the brain may represent a primary causal factor in depression. However, it should be noted that psychological factors are of utmost importance with regard to HPA regulation. The HPA axis is extraordinarily sensitive to environmental factors. Psychological factors (such as perception of negative social evaluation

of oneself) determine the magnitude of a stress-related cortisol response. Clinicians and investigators have long wondered whether cortisol alterations in depression are a neuroendocrine response to psychological suffering (i.e., depression causes HPA disturbance), or whether HPA hyperactivity triggers depressive symptoms (i.e., HPA disturbance causes depression). In fact, chronically elevated cortisol levels (e.g., due to a pituitary tumor as in Cushing's syndrome) can bring on aspects of depression. However, these polarized causal views are oversimplified. In general, neither cortisol alterations nor distress should be conceptualized as the primary causal factor in depression. Instead, the neural mechanisms associated with HPA dysregulation are intimately intertwined with the mechanisms that underlie psychological processes involved in major depressive disorder. Further research is needed to show how the dynamics of the HPA in depression are not merely a cause, or an effect, or an underlying feature of depression, but how they are intimately connected to the psychological features, self-disparagement, and suffering that characterize the phenomenological and behavioral aspects of depression.

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See also

Biological Models of Depression
[MH46] Brain Circuitry
Cortisol
Hormones
Hypothalamic-Pituitary-Thyroid Axis

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Hypothalamic-Pituitary-Thyroid Axis

As early as the late 19th century, clinicians recognized that disruptions of the hypothalamic-pituitary-thyroid (HPT) axis were associated with mood disorders. The relationship between HPT-axis disruption and psychiatric morbidity has been among the most scrutinized of the endocrine axes, second only to the hypothalamic-pituitary-adrenal (HPA) axis. As HPT-axis disturbances are corrected, psychiatric symptoms also tend to abate.

The HPT axis consists of the hypothalamus, the anterior pituitary gland (adenohypophysis), and the thyroid gland. The