

Hypothalamic-Pituitary-Adrenocortical Axis: Neuropsychiatric Aspects

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ABSTRACT

Evidence of aberrant hypothalamic-pituitary-adrenocortical (HPA) activity in many psychiatric disorders, although not universal, has sparked long-standing interest in HPA hormones as biomarkers of disease or treatment response. HPA activity may be chronically elevated in melancholic depression, panic disorder, obsessive-compulsive disorder, and schizophrenia. The HPA axis may be more reactive to stress in social anxiety disorder and autism spectrum disorders. In contrast, HPA activity is more likely to be low in PTSD and atypical depression. Antidepressants are widely considered to inhibit HPA activity, although inhibition is not unanimously reported in the literature. There is evidence, also uneven, that the mood stabilizers lithium and carbamazepine have the potential to augment HPA measures, while benzodiazepines, atypical antipsychotics, and to some extent, typical antipsychotics have the potential to inhibit HPA activity. Currently, the most reliable use of HPA measures in most disorders is to predict the likelihood of relapse, although changes in HPA activity have also been proposed to play a role in the clinical benefits of psychiatric treatments. Greater attention to patient heterogeneity and more consistent approaches to assessing treatment effects on HPA function may solidify the value of HPA measures in predicting treatment response or developing novel strategies to manage psychiatric disease. © 2014 American Physiological Society. *Compr Physiol* 4:715-738, 2014.

Introduction and Overview of Normal HPA Axis Regulation

Investigation of abnormal activity of the hypothalamic-pituitary-adrenocortical (HPA) axis in neuropsychiatric disorders now dates back at least 60 years. This article will cover evidence for disruption of HPA function in mental health disorders, the effects of psychotropic medications on HPA activity, and the possibility that altered HPA activity contributes to as well as reflects psychiatric disease. To the extent that animal research potentially fills in gaps in our knowledge, these data will be included; however, because of the uncertainties in modeling neuropsychiatric disease in animals, the focus will be on human studies.

The HPA axis is a neuroendocrine system for regulating adrenocortical secretion of glucocorticoid steroids by the brain. Interest in the relationship between the HPA axis and neuropsychiatric disorders is logical given the regulation of this axis by factors that are frequently abnormal in psychiatric disease, including stress responses, circadian rhythms, and glucocorticoid signaling. Afferent projections to hypothalamic neurons elicit the release of corticotropin-releasing hormone (CRH), vasopressin, or oxytocin. These hypothalamic hormones stimulate corticotroph cells in the anterior pituitary to secrete adrenocorticotropin (ACTH). Vasopressin and oxytocin are weaker ACTH secretagogues than CRH, but can synergize with CRH to elicit even greater ACTH secretion than CRH alone (247,316). ACTH activates the synthesis and secretion of glucocorticoid cortisol by the human adrenal cortex. The trophic effects of ACTH result in adrenal

hypertrophy and greater cortisol secretion after prolonged stimulation (403). Glucocorticoids in turn regulate their own secretion by feedback inhibition, reducing the synthesis and secretion of CRH, vasopressin, and ACTH, but probably not oxytocin (103, 117, 458). The multiplicity of releasing factors, along with the variety of their combination and regulation by glucocorticoid feedback, would be expected to maximize the flexibility and dynamic range of HPA responses to stimulation.

This versatility in responsiveness is critical for the well-known and reliable activation of the HPA axis by stress. Stress can be defined as any actual (physical) or perceived (psychological) threat to the well-being of an organism, and may be acute and brief or chronic and prolonged. Mounting and terminating HPA responses to stress are both key to physical and psychological health. Glucocorticoids have potent effects on immune, cardiovascular, metabolic, and mental function that facilitate restoring homeostasis after short-term stress. However, sustained elevations in glucocorticoids can have adverse immunosuppressive, hypertensive, diabetic, and cognitive effects (349). Such prolonged elevations indicate either anomalous HPA regulation or another underlying disease requiring treatment.

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Independently of stress, the HPA axis is also activated on a daily basis in a circadian rhythm ultimately governed by activity of the hypothalamic suprachiasmatic nucleus (201). Glucocorticoid secretion closely follows the activity cycle, with highest levels occurring just before waking, corresponding to early morning in diurnally active humans (110, 201). The circadian rhythm in glucocorticoids requires the presence of, but not circadian variations in, CRH (279). Circadian increases in glucocorticoid secretion also depend on increases in adrenal responsiveness to ACTH that are at least partly mediated by changes in adrenal nerve activity (110). The circadian rise in glucocorticoids likely accounts for the “permissive” effects of glucocorticoids on physiological and CNS functions, that is, effects that do not require stress-induced increases in glucocorticoid secretion (349). Disturbances in circadian cortisol rhythms have increasingly been linked with the adverse metabolic, cardiovascular, and cognitive effects of glucocorticoid excess (21).

Other than cessation of the neural activity generated by stress-induced or circadian stimuli, glucocorticoid negative feedback is the only mechanism for reducing HPA activity. Adrenal glucocorticoids bind to two receptors, a lower affinity glucocorticoid receptor (GR) and a higher affinity mineralocorticoid receptor (MR), both of which are involved in glucocorticoid feedback inhibition. These receptors are collectively referred to as corticosteroid receptors. In addition to their peripheral expression, MR are expressed in discrete areas of the brain, primarily in limbic regions. GR are more ubiquitously expressed in the brain as well as in corticotrophs and the rest of the body (90). Because of their higher affinity, MR mediate feedback inhibition at low glucocorticoid levels, such as during the circadian trough (90). GR mediate feedback effects of elevated glucocorticoids, such as during stress or at the circadian peak, although this feedback is not exclusive to GR and can involve MR as well (90, 301). By virtue of expressing the higher affinity MR, the brain is a more important site for feedback inhibition by naturally occurring glucocorticoids such as cortisol (238). However, access to or retention by the brain of some synthetic glucocorticoids such as dexamethasone may be limited, potentially making the corticotroph a more important target for the HPA-suppressing actions of these synthetic steroids (306).

CNS glucocorticoid actions can be influenced by factors that regulate steroid access to MR and GR. As alluded to above, the multidrug resistance protein/ p-glycoprotein membrane transporters actively exclude steroids from cells and reduce or delay CNS penetration of synthetic steroids like dexamethasone (271, 306, 445). The type 1 and type 2 isoforms of 11 β -hydroxysteroid dehydrogenase can enhance or diminish levels of endogenous glucocorticoids available to bind MR or GR by respectively converting the inactive metabolite cortisone to cortisol or inactivating cortisol to cortisone (443). Increases in ACTH after 11 β -hydroxysteroid dehydrogenase inhibition indicate that generation of active cortisol by type 1 11 β -hydroxysteroid dehydrogenase contributes to normal feedback regulation of HPA activity in humans (332). In

addition to preventing excess sodium retention by cortisol-induced MR activation, the type 2 11 β -hydroxysteroid dehydrogenase is likely to protect the developing brain from programming effects of glucocorticoids (443).

There is also increasing evidence for nongenomic mechanisms of glucocorticoid regulation of HPA activity (113). Rapid glucocorticoid inhibition of CRH and vasopressin secretion by neurons of the paraventricular hypothalamus has been shown to be mediated by endocannabinoids, membrane-derived lipids that act as retrograde transmitters (101, 167). Glucocorticoid binding to an as-yet incompletely characterized receptor in the postsynaptic membrane results in the release of the endocannabinoids anandamide and/or 2-arachidonoylglycerol. Endocannabinoid binding to G protein-coupled CB1 receptors, the predominant endocannabinoid receptor in brain, results in inhibition of presynaptic neurotransmitter release via decreases in cAMP (167). Endocannabinoid-mediated mechanisms have been demonstrated for glucocorticoid action at the prefrontal cortex, amygdala, and possibly the hippocampus for extrahypothalamic regulation of HPA activity (167). Glucocorticoids have also been shown to inhibit organic cation transporter monoamine uptake in the hypothalamus (128), although the implications of this effect for HPA regulation have yet to be defined. Glucocorticoid effects in brain are not restricted to HPA feedback control, and as mentioned above, glucocorticoids also have well-recognized effects on mental function. The relevance of these effects to neuropsychiatric disorders will be discussed below.

HPA Axis Dysregulation in Neuropsychiatric Disorders

Depression

Disruption of HPA function in depression has attracted the most consistent and long-standing attention. Abnormal HPA activity was reported in depressed patients as early as 1949 [reviewed in (115)], with an expanding number of publications over the years as methods for characterizing HPA function and depression were increased and refined. The prevailing picture emerging from this work is that HPA activity is increased in major depression. Although the incidence of elevated HPA activity in depression has been reported to rise with increasing age (159) (222), there is not agreement on this issue (223, 309, 386), and HPA hyperactivity is not certainly not exclusive to older individuals (177). Basal plasma cortisol and ACTH levels can be increased, either at both the circadian trough and peak (98, 246, 277, 352, 423, 446) or primarily during the circadian trough, corresponding to the late afternoon or early evening period in humans (278, 454). Analysis of ultradian features of the circadian rhythm has further revealed that hypercortisolism in depressed patients is associated more with an increased amplitude but not frequency of cortisol pulses (246). Depressed patients exhibit more disorder or randomness in ACTH or cortisol secretory pulses

(446,457), also suggestive of dysregulation. Consistent with sustained increases in pituitary-adrenal activity, elevations in 24 h urinary free cortisol occur in depression (203,331,363). Reported increases in adrenal size (285,337) likely reflect the sustained effects of increased ACTH release. CSF CRH has also been found to be elevated in depressed patients (25,442), although it should be noted that there are extrahypothalamic as well as hypothalamic sources of CRH (351,383) that may contribute to this measurement.

These increases in HPA activity, resembling and sometimes overlapping those due to tumors in Cushing's syndrome, led to the use of the dexamethasone suppression test (DST) in psychiatry to determine if, as in Cushing's, there was glucocorticoid-independent drive of the HPA axis in depression (57). In most healthy subjects, administration of a relatively low dose of the synthetic glucocorticoid dexamethasone (1-1.5 mg) at 11 pm suppresses plasma cortisol below 5 µg/dL until at least 3 pm the next day (177,324). Widespread reports of nonsuppression or early escape from suppression by dexamethasone have been interpreted to indicate pathophysiological drive or impaired glucocorticoid sensitivity of the HPA axis in depression (16,324,336,362).

The combined dex/CRH test, in which intravenous CRH administration after dexamethasone suppression reveals abnormal brain drive to the pituitary, has proven more sensitive in detecting enhanced HPA activity in depression. ACTH is elevated in the dex/CRH test in at least 80% of depressed patients (184,222,362). Psychotic (73,119,207,284) and bipolar (manic-depressive) depression (63,86,245,393,432) have particularly consistent evidence of elevated HPA activity in the basal state, after dexamethasone, and in the combined CRH/dex test (16,66,459). This higher incidence of elevated HPA activity can be related to disease severity, but this relationship is not strong (59,284,386). There is disagreement as to whether HPA activity is increased in purely manic phases of bipolar depression (63,86,245,345), but the presence of depression or negative affect is more commonly associated with HPA hyperactivity in bipolar depression (393,411,432).

However, the evidence for HPA hyperactivity in depression is not without its contradictions. Numerous publications find no differences in HPA measures between depressed and normal subjects [for example, (112,333,429,431,433,455)]. Although depressed subjects might also be expected to exhibit enhanced responses to experimental stressors, this expectation is not borne out. Although female gender and comorbid anxiety may enhance responses (65,456), cortisol or ACTH responses to psychological or physical stimuli have generally been found to be similar between depressed and healthy subjects (133,215,456). Early reports that HPA responses to hypoglycemia were blunted in depression (58) may have been confounded by insulin resistance, which has been correlated with elevated cortisol in depressed patients (282). Only approximately 45% of all depressed patients exhibit DST non-suppression (16,177,324). DST results are not consistent within individuals (96), although it should be noted that

plasma dexamethasone was not measured to ensure similar dexamethasone levels in all tests. Despite its higher sensitivity, the CRH/dex test does not detect abnormal HPA function in 20% of depressed patients (159). Debate continues as to whether the patients not picked up by these tests represent limitations of the testing methodology or distinct subtypes of depression. A recent meta-analysis concluded that variations in both methodology and patient characteristics limit the strength of the association between HPA hyperactivity and depression (386).

Supporting the possibility that patient heterogeneity influences HPA findings in depression, there is an intriguing body of literature that patients with atypical depression are more likely to have normal or even reduced levels of HPA activity than are patients with melancholic depression (136,386). The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders lists melancholic features as including (but not limited to) persistent inability to feel or express pleasure, weight or appetite loss, and disturbed sleep. In contrast, atypical depression, so-named to distinguish it from melancholic depression, can be characterized by the capacity for positive mood, increased appetite or weight gain, and increased sleep (11). Atypical depression has also been associated with an earlier onset and more chronic disease course, whereas melancholic depression is more episodic in nature (387). There is ongoing contention about whether DSM guidelines are appropriate to distinguish the atypical subtype, and whether features such as anxiety, age of onset, and disease chronicity should be added or substituted for the current criteria (307,389,398,402). Nevertheless, a number of studies [though not all (61,372)] provide evidence of reduced HPA activity in atypical depression (136), including lower cortisol levels (15), greater sensitivity to dexamethasone suppression (240,388), and lower CSF CRH levels (131). Other studies indicate that HPA activity is at least not elevated in atypical depression (455). Atypical depression comprises 15% to 35% of all depressed patients (398), consistent with the percentage of patients that lack enhanced pituitary-adrenal responses to the DST or dex/CRH test. Indeed, the percentage of patients with atypical or melancholic depression included in a study has been found to influence the likelihood of detecting increased HPA activity in depression (386). Thus, HPA activity may reflect a continuum of dysfunction in depression ranging from enhanced activity in the "typical" or melancholic subtype to reduced activity in the atypical subtype, with subtypes with normal HPA function in between that may yet be defined.

Anxiety disorders

As with depression, there is notable albeit inconsistent evidence of HPA hyperactivity in a variety of anxiety disorders, including panic disorder, generalized anxiety disorder, and social anxiety disorder. There is common agreement that panic disorder can be differentiated from generalized anxiety disorder in being more likely to be heritable, occur in females,

and be co-morbid with depression (217,265). The preponderance of the evidence indicates that elevated HPA activity is more likely in panic disorder than in generalized anxiety disorder (2,43,54,111,176,217,265,358,424), although there are exceptions to these findings (43,54,169,208,235,313,359), possibly due to variability in illness severity (24). Abnormally high basal or postdexamethasone cortisol levels in panic disorder can be separated from the effects of depression (80,203). High basal levels of HPA activity make it difficult to determine if the axis is more sensitive to non-psychological stimuli (287). Although HPA responses to hypoglycemia have been reported to be attenuated in panic disorder (196), these results are open to question since glucose clamp techniques were not used and glucose may have been higher (and the hypoglycemic stimulus lower) in the panic disorder subjects. However, panic attacks can be dissociated from HPA activity, in that panic can be induced without stimulating the HPA axis, and HPA stimulation does not necessarily produce panic [(4) and references therein]. In one study, higher baseline plasma cortisol levels both predicted and correlated with the severity of panic attacks induced by lactate infusion (76). However, other studies have found no differences between panic disorder and healthy subjects in a variety of HPA measures (4,43,54,265,422).

Basal HPA activity also appears to be unaffected in social anxiety disorder (71,221,264,328,413,415), although HPA responses to socially relevant stresses such as public speaking are typically increased (71,328,415). HPA responses to physical stresses such as exercise are unchanged (123). Contradictory findings (221,264,265) may be due to patient heterogeneity. Social phobics have been found to exhibit cortisol responses to public speaking stress that were either greater than or similar to those of controls (123); unknown percentages of patients with these two types of responses could account for disparate findings in other studies.

It has been proposed that the higher incidence of abnormal HPA activity in panic disorder is due to the greater sensitivity of these individuals to threatening or unfamiliar situations (4). There is limited evidence to suggest that this sensitivity is an intrinsic trait of panic disorder, present even patients who have been asymptomatic and drug-free for over 6 months (241). When panic disorder patients were blinded to whether they would receive a panicogenic agent, or were given instructions on preparing for or controlling the effects of the agent, both symptomatic and ACTH responses to the panic-inducing stimuli were prevented (4).

In the context of these findings, the variability in HPA activity found in many anxiety disorders may be attributable to variability in controlling the stressfulness of experimental testing conditions (4). For example, the failure to detect differences in HPA function between social anxiety disorder and control subjects by salivary cortisol sampling at home (264,413) could be due to the familiarity of the environment, whereas studies detecting significant HPA reactivity in social anxiety disorder used verbal math and extemporaneous speaking tests in a laboratory setting (71,328), a paradigm

that potentially conveys greater social threat. Studies not reporting altered HPA responses to public speaking stress in social phobics either did not control for time of day or allowed subjects to give a preprepared speech from notes (237,264), factors that could respectively have obscured incremental HPA stress responses or reduced the subjective threat level of the testing conditions.

Posttraumatic stress disorder

Originally categorized as an anxiety disorder, posttraumatic stress disorder (PTSD) is considered separately here not only because it is now classified separately in the DSM V (10,11), but also because the prevailing picture of HPA function in PTSD differs dramatically from that of other anxiety disorders or of the majority of depressed patients. PTSD is characterized by a hypervigilant state in which there are uncontrolled, intrusive memories of traumatic events, typically associated with heightened autonomic and anxiety responses (11). Remarkably, despite over 50% comorbidity of PTSD with depression or anxiety disorders (40), HPA activity is predominantly reduced, rather than enhanced, in PTSD. This phenomenon, originally reported in 1986 (267), has been extensively investigated by Yehuda and colleagues. CSF CRH levels may be increased in PTSD [but see (35)], while basal cortisol levels are usually reduced or unexpectedly normal relative to central CRH (450). Lower cortisol levels in PTSD are associated with a longer period of low cortisol secretion at the circadian nadir and a shorter period of circadian peak cortisol secretion (446). Also in contrast to depression, ACTH responses to CRH or the dex/CRH test have been found to be suppressed relative to those in healthy controls (391).

Lower basal cortisol levels in PTSD are most likely attributable to an increased sensitivity of the HPA axis to glucocorticoid feedback rather than to secondary or primary adrenocortical insufficiency. Although seemingly contradictory to the pattern of low HPA activity described for PTSD, HPA activity prior to or during trauma recall is often augmented in PTSD (109,134,150,242,450), indicating that HPA responses to challenge are not impaired. Since cortisol has been found to be lower in the absence of provocative testing, the higher cortisol levels associated with these experimental stimuli have been interpreted as resulting from the stress of anticipation or trauma-specific reminders, rather than to chronic elevations in HPA activity (47).

There is ample [although not universal (425)] evidence of greater sensitivity to dexamethasone or cortisol feedback inhibition in PTSD (450). Also consistent with greater HPA sensitivity to changes in cortisol, PTSD patients exhibit significantly less randomness in ultradian cortisol pulses than do normal subjects (446) and rapidly normalize elevated cortisol levels stimulated by trauma recall (109). Increased numbers and sensitivity of peripheral leukocyte GR to glucocorticoids have also been demonstrated *in vitro*, suggesting that alterations in GR sensitivity may occur throughout the body in PTSD (450,452). MR function, however, appears to be normal (297).

Obsessive-compulsive disorder

HPA function has also been evaluated in obsessive-compulsive disorder (OCD), in which there is uncontrollable, neurotic repetition of behaviors such as hand-washing (11). Single-point measurements of basal cortisol or ACTH have generally not revealed any differences between OCD and normal subjects (41, 64, 171, 212, 254, 344, 439). However, several studies measuring either cortisol at multiple time points throughout the day or 24 h urinary free cortisol have detected evidence of basal elevated HPA activity (130, 146, 218, 277). Studies that did not find alterations in HPA activity with circadian sampling in OCD did not use remote blood sampling techniques (275), so it is possible that the effects of sleep disruption obscured OCD-related differences. Elevated CSF CRH has also been reported in OCD (8), although as in depression, the significance of extrahypothalamic CRH contributions to this measurement remains to be determined. The majority of dexamethasone suppression studies have found OCD patients to exhibit normal suppression or inconsistent nonsuppression with repeat testing (82, 183, 253); only one study has reported elevated postdexamethasone cortisol levels in OCD (62). Thus, the available data suggest that there may be enhanced basal drive but normal glucocorticoid feedback regulation of the HPA axis in OCD.

Interestingly, therapeutic exposure of OCD subjects to stimuli designed to provoke compulsive behaviors elicits robust increases in subjective ratings of stress without stimulating significant HPA activity [(209) and citations therein]. It is currently unknown if this apparent impairment of the HPA response can be attributed to inhibition by elevated basal levels or cortisol, or whether, as has been theorized for PTSD (447, 450), the lack of HPA reactivity has implications for the development of OCD. Further studies including healthy controls and other experimental challenges are necessary to evaluate the significance of these findings.

Since depression is often comorbid with OCD, the extent to which HPA alterations reflect concurrent depression remains uncertain. Some studies have suggested that higher HPA activity in OCD correlates with depression symptoms (183, 275), while others have found that elevated HPA measures are independent of the presence or severity of depression (8, 62, 218). As with depression, alterations in HPA activity do not correspond well with disease severity in OCD (8, 62, 82, 130, 146, 183).

Schizophrenia

HPA function has also been analyzed in schizophrenia, with more mixed results. Although there is evidence for increased HPA activity in schizophrenia, possibly related to reduced corticosteroid receptor expression (39, 144, 311, 427, 437, 444), a recent review has concluded that this is not a consistent finding (39). The incidence of augmented HPA activity appears to be highest in first-episode patients (39, 145, 340). Where HPA hyperactivity or dexamethasone nonsuppression was observed, it was difficult to relate to negative (withdrawal)

or positive (hallucination) symptoms, although there may be a better correlation with negative symptoms in long-standing schizophrenia (39, 202, 369, 461).

While it has been proposed that some of the baseline elevations in HPA activity might be attributable to greater stress sensitivity in schizophrenia (39), the most striking and consistent HPA alteration observed in schizophrenia is actually a reduction in cortisol and ACTH responses to psychological stress. Public speaking elicits less of an increment in cortisol and ACTH in schizophrenic patients than in healthy controls (39, 191, 414). HPA sensitivity to physical stressors like exercise, hypoglycemia, or 2-deoxyglucose-induced neuroglycopenia has been found to be normal (108, 191, 204, 414) or possibly even enhanced (51) in schizophrenia. This selective blunting of responses to psychological stress is not attributable to differential feedback inhibition from differing baseline cortisol levels because prestress cortisol levels in all but one of these studies were similar between groups (48, 108, 191, 414). Autonomic responses and subjective anxiety ratings have been shown to be at least as high in schizophrenic patients as in controls (48, 191, 414), indicating that there were no general deficits in processing or responding to psychological stimuli. Although antipsychotic drugs may inhibit HPA activity (see below), medication seems unlikely to account for the effects on psychological stress responding because similar blunting is seen in drug-naïve schizophrenic subjects (414). The pathways responsible for this psychological stress-related defect in HPA activation could provide useful insights into the neuropathology of schizophrenia.

Autism spectrum disorders

Interest in HPA activity in autism has been sparked by observations that behavior is either stress-like or exacerbated by stress in this disorder (231). Autism spectrum disorders are characterized as neurodevelopmental disorders with impaired communicative and social functioning and rigid, repetitive patterns of behavior. The degree of impairment can be severe and associated with mental retardation, or it can be slight, encompassing the designations of high-functioning autism or Asperger's Syndrome (11). Because the disease typically presents in early in life, a larger proportion of the HPA studies reviewed here are in children. HPA findings in autism spectrum disorders have largely been inconclusive. The majority of studies have found no differences between autistic individuals and healthy controls in basal cortisol and ACTH levels at various times in the circadian cycle (13, 49, 213, 231, 292, 325, 381, 419, 462), although slight reductions in the normal morning rise in cortisol have been noted (49). Dexamethasone non-suppression has been found slightly more frequently than normal suppression in autistic subjects, but normal cortisol suppression rates are still close to 50% (74, 178, 194). Significantly higher levels of morning pituitary-adrenal activity have been correlated with autism severity (406), while significantly lower levels of daytime cortisol have been correlated with repetitive behavior (124),

suggesting the need for more detailed classification of autism spectrum subjects to reconcile discrepant HPA data. However, other studies have found no correlation of HPA hormones with autism symptoms, including during therapy-related improvements in behavior (84, 419).

Several studies have reported elevated HPA responses to stress in autism spectrum disorders, and these results may also offer insight into the conflicting findings regarding basal HPA activity. Autistic individuals have been found to exhibit higher salivary cortisol levels after a variety of social and nonsocial stressors, including venipuncture, mock MRI exposure, and public speech and math tests (77, 78, 381, 406). Not all investigations have confirmed this enhanced HPA reactivity to stress (74, 192, 232), however, and it has been proposed that the greater variability in HPA responses to stress reflects a higher stress sensitivity in autism spectrum disorders (231, 406). In particular, elevated plasma ACTH without concomitant increases in cortisol have been interpreted to indicate acute stress reactivity independent of chronic HPA axis hyperactivity (231, 406). Notably, all studies reporting elevations in basal HPA activity in autistic subjects found increased plasma ACTH (84, 187, 396, 406), with only one study also finding elevations in cortisol (187). Interestingly, all studies reporting elevated basal HPA activity also used venipuncture to assess hormone levels, whereas the almost all studies not reporting increases in autistic subjects used salivary or urinary sampling to measure cortisol levels (13, 49, 77, 213, 232, 325, 381, 419, 462). It therefore seems plausible, if venipuncture can elicit significantly higher HPA responses in autistic individuals (381), that it might artifactually increase HPA hormones in otherwise basal conditions. Similar concerns might apply to reports of dexamethasone nonsuppression in autistic children (74). Studies using venipuncture that did not find elevated HPA activity included a large proportion of adolescents or adults (84, 192, 292), who are less likely than children to find blood sampling stressful. Consequently, other than greater stress reactivity, HPA function is unlikely to be altered in autism spectrum disorders.

Effects of Neuropsychiatric Treatments on the HPA Axis

Antidepressants

A wide variety of depression treatments have been reported to decrease pituitary-adrenal hyperactivity in depression, including tricyclic antidepressants (99, 225, 274, 294, 378, 423), selective serotonin reuptake inhibitors [SSRIs; (181, 289, 290, 294, 390)], the dopamine reuptake inhibitor bupropion (390), the α_2 -adrenergic antagonist mirtazapine (177, 229, 352), electroconvulsive shock (222, 294), and interpersonal counseling (116, 365, 399). DST nonsuppression and enhanced ACTH responses to the CRH/dex test typically resolve (16, 184, 246, 324) with antidepressant response (defined as a 50% reduction in depression score) or remission (defined as a depression score in range of healthy controls, typically below

7 on the Hamilton Depression Rating Scale). Abnormalities in the circadian secretion of HPA hormones are also typically reversed by successful treatment (246). Successful antidepressant treatment resulting in either response or recovery has also been associated with a reduction in both adrenal gland volume (337) and cortisol responses to ACTH (12, 362, 397), indicating diminished chronic adrenocortical stimulation. Antidepressants and ECT have also been shown to decrease CSF CRH levels, although these studies lack data to determine if CSF CRH was elevated in the depressed subjects before treatment (88, 160, 291). Where longitudinal studies have been performed, normalization of HPA activity in both the dexamethasone suppression (172) and dex/CRH tests (185) has been found to occur 2 to 3 weeks before significant clinical improvement, which has raised interest in the possibility, discussed below, that HPA activity could serve as a biomarker of antidepressant response.

These studies notwithstanding, there are numerous contradictions to the concept that antidepressants all inhibit HPA activity. Many studies find no change in HPA endpoints after successful treatment with tricyclic antidepressants (26, 181, 272, 333, 378), SSRIs (31, 99, 181, 205, 278, 333), or the combined norepinephrine/serotonin reuptake inhibitors venlafaxine and duloxetine (18, 127, 429). There are even reports that HPA activity is enhanced after treatment with monoamine oxidase inhibitors (273, 385) or SSRIs (56, 151, 272, 343). Similarly disparate antidepressant effects have been described in healthy volunteers, including decreases (276, 361, 418), increases (92, 151, 193, 374, 409), or no change (149, 220) in HPA activity, but most of these studies used only acute or short-term (<1 week) administration. In the few studies in which more than a week of treatment was assessed in healthy individuals, HPA activity was found either to be unaffected (236, 350) or enhanced (56, 385). Although some of the discrepant effects might be attributable to differences in drugs within a given class of antidepressants or to different effects on neurotransmitters such as serotonin, which can have either stimulatory or inhibitory effects on HPA activity (252), in many cases conflicting effects have been reported with the same medication [for example, (31, 99, 151, 181, 272, 274, 289, 290, 294, 333, 378, 390)]. It is, therefore, likely that contradictory results may also be due to differences in treatment time or experimental techniques; the possibility that patient heterogeneity contributes to variability in antidepressant effects is discussed below.

Mood stabilizers

Mood stabilizers can be divided roughly into lithium and anticonvulsants. These drugs are approved to treat bipolar depression, although off-label use of anticonvulsants has been tested to treat anxiety disorders (323) and PTSD (436). The mechanisms by which these drugs influence mood, or potentially the HPA axis, remain unclear. Lithium has been reported, although not consistently, to augment HPA activity. Chronic lithium administration can enhance ACTH responses

to the dex/CRH test (5, 52, 223, 433). Lithium has also been found to increase cortisol responses to the serotonin precursor 5-hydroxytryptophan (273). Lithium enhancement of HPA activity has (52, 433), although not consistently (273), been correlated with clinical response to lithium and may be due to lithium-induced increases in vasopressin (433), which would synergize with CRH in stimulating ACTH release. In contrast, two studies have found decreases in basal cortisol levels after lithium treatment (341, 375). This apparently inhibitory effect of lithium is difficult to reconcile with the enhancing effects found in the other studies, and cannot be readily attributed to differences in study populations, treatment time, or clinical outcome. Since the dex/CRH studies finding that lithium heightened HPA activity did not assess cortisol in the absence of dexamethasone, it remains to be determined if lithium has additional effects on basal cortisol production that might be detected at different times of day or with different techniques. Lithium seems to have little effect on the HPA axis of psychiatrically normal subjects after 2 to 4 weeks of administration (27, 28, 260).

Of the anticonvulsants, carbamazepine is the most widely recognized to have effects on HPA activity, although these effects are unrelated to clinical efficacy. As an inducer of the Cyp3A4 P₄₅₀ enzyme responsible for corticosteroid metabolism (30, 223), carbamazepine can artifactually increase dexamethasone nonsuppression or augment ACTH responses in the dex/CRH test by promoting dexamethasone clearance (206, 223, 318). Carbamazepine has also been reported to increase free as well as total plasma cortisol in normal subjects (310). Carbamazepine has been reported to have vasopressin-like actions to increase water retention that can inhibit endogenous vasopressin (342), thus potentially diminishing ACTH-releasing factors that could synergize with CRH. These opposing effects may account for other reports that carbamazepine did not affect basal HPA activity (186, 341). The related compound oxcarbazepine may have similar actions to increase steroid clearance and inhibit vasopressin (30, 170, 342), although limited available data suggest that oxcarbazepine does not affect basal morning cortisol levels (55). There is some evidence that acute administration of lamotrigine and valproic acid can inhibit HPA responses to stimulation in normal subjects (258, 318), but the chronic effects of these drugs on basal HPA activity are inconclusive and do not appear to be robust (318, 368).

Anxiolytics

This classification encompasses benzodiazepines and buspirone, although anxiety disorders are now more frequently treated with antidepressants (114). Data on buspirone are limited. Although it is used as an acute challenge to stimulate corticosterone secretion as an index of serotonergic tone [e.g., (304)], buspirone has not been found to have any effects on HPA activity after chronic treatment (67).

Benzodiazepines have predominantly inhibitory effects on HPA activity, demonstrated in the vast majority of studies with

acute administration in normal subjects. Benzodiazepines can inhibit basal circadian peak (morning) as well as nadir (evening) ACTH and cortisol levels (140, 175, 317, 334, 360). Lack of acute suppressive effects on basal HPA activity is usually associated with the use of diazepam (46, 152, 228, 312); alprazolam has been suggested to be a more potent inhibitor of HPA activity (19). The benzodiazepine alprazolam has also been found to reduce increases in HPA activity resulting from relief of glucocorticoid feedback inhibition by either the MR antagonist sodium canrenoate or the glucocorticoid synthesis inhibitor metyrapone (142, 143). Benzodiazepines significantly attenuate HPA responses to stressors ranging from public speaking (121) and viewing violent images (347) to exercise (70, 100), serotonergic agonists (364), 2-deoxyglucose-induced neuroglycopenia (44), hypoglycemia (132, 152, 312), and abdominal surgery (95). Exceptions to the reliable ability of benzodiazepines to inhibit stimulated HPA activity acutely (9) may be due to longer intervals between drug administration and the experimental stimulus. In addition to acting at central GABA_A receptors to inhibit CRH responses to stimulation (97, 318), benzodiazepines have also been reported to inhibit ACTH responses to vasopressin and CRH (219, 408). Negative findings in this regard (143, 329) may be due to use of lower benzodiazepine doses. There is also evidence that benzodiazepines can inhibit adrenocortical sensitivity to ACTH (143, 407); this inhibition is likely to be mediated by central or peripheral nerves rather than peripheral benzodiazepine receptors in the adrenal (now known as the outer mitochondrial membrane translocator protein, or TSPO) because the latter facilitate rather than inhibit corticosteroid synthesis (303).

The ability of chronic benzodiazepine treatment to decrease HPA activity in mood disorders is more controversial. Several studies have shown no (81, 217) or at most subtle (85) changes in HPA endpoints after 4 to 9 weeks of alprazolam or diazepam treatment panic or generalized anxiety disorder. Nevertheless, consonant with the acute inhibitory effects of these drugs, there are also several reports that alprazolam or diazepam decreased cortisol secretion in panic patients (3, 217, 250) and in major depression (348). However, even when HPA inhibition has been found after long-term benzodiazepine use, it did not correlate with clinical improvement (3, 348).

Antipsychotics

The two main classes of antipsychotics, typical and atypical, are distinguished by the greater affinity of atypical antipsychotics for 5HT_{2A} and 5HT_{2C} serotonin receptors (346). Antipsychotics are used primarily in the treatment of schizophrenia and other psychotic disorders, although some atypical antipsychotics have been approved for bipolar depression and as a supplement to antidepressant treatment of unipolar depression (72). Antipsychotics have also been tested experimentally for treatment-resistant anxiety disorders (114, 323) and PTSD (436).

Antipsychotics have been thought to have little effect on HPA hormones (202, 268), but there is substantial evidence that both typical and atypical antipsychotics can suppress basal and stimulated HPA activity (427). Acute administration of the typical antipsychotic haloperidol (155) or the atypical antipsychotics olanzapine, quetiapine, or ziprasidone (68, 69, 270) has been reported to inhibit circadian peak, circadian trough, and heat or noise stress-induced cortisol secretion. Short-term administration of haloperidol for 3 days has been found to reduce morning, afternoon, and evening plasma cortisol levels in manic patients (75). Slightly longer (8 day) treatment with olanzapine also reduced nocturnal cortisol in normal subjects (420). Chronic treatment (≥ 1 month) with typical or atypical antipsychotics, only reported in schizophrenic patients, has further been shown to reduce both morning and nocturnal cortisol levels (261, 262, 298, 356, 395, 440, 461). Withdrawal of schizophrenic subjects from haloperidol treatment has been found to increase CSF CRH levels, consistent with a tonic suppressive effect of haloperidol on central CRH systems (120).

Exceptions to the inhibitory effects of antipsychotics on HPA activity include several studies finding no effect on basal ACTH or cortisol (45, 69, 91, 118, 189, 200, 335, 465), and a few studies reporting stimulatory effects (42, 189, 280). Most of the negative studies used typical antipsychotics such as haloperidol or trifluoperazine (69, 91, 118, 200, 335, 465); atypical antipsychotics are thought to have more potent inhibitory effects on the HPA axis through their antagonism of 5HT₂ serotonin receptors (39, 69, 200, 270). Of the two studies finding no effect of chronic atypical antipsychotics on HPA function in schizophrenia, no or only a 7-day drug washout period was specified before study (45, 189), whereas most studies finding significant inhibitory effects used a minimum drug-free period of 2 weeks (200, 298, 395, 440, 461). Thus, the possibility that study effects could not be discriminated from the inhibitory effects of prior antipsychotic medication cannot be excluded. Findings of increased HPA activity after antipsychotic treatment are harder to explain, but all involved small numbers of subjects (≤ 10) and used typical antipsychotics, which may be less effective at inhibiting the HPA axis. In one study of healthy volunteers, adverse effects were noted in 2/6 subjects, raising the possibility that stress from side effects could have accounted for enhanced HPA responses. In sum, however, it seems likely that both atypical and typical antipsychotics can have inhibitory effects on HPA activity that should be factored into interpretations of patient hormonal data.

Significance of HPA Dysregulation in Psychiatric Disease

Given the well-known endocrine consequences of inappropriate glucocorticoid secretion, aberrant HPA activity in psychiatric disorders could have adverse effects on general health. It is widely appreciated that depression can worsen the course and prognosis of chronic diseases such as heart disease,

stroke, diabetes, cancer, and respiratory and renal disease (105, 122, 148, 211, 234, 302), and emerging evidence suggests that a similar relationship likely exists for cardiovascular and metabolic disease in other psychiatric disorders (39, 104, 314, 315, 405). The ability of glucocorticoids to promote diabetes, hypertension, and immune suppression (349) potentially incriminates the HPA axis in these disease interactions; inflammatory processes have also been suggested to be relevant to depression in which glucocorticoids are low (300). In addition, glucocorticoids affect attention and memory retrieval (93) in a manner that could account for some of the cognitive deficits reported in depression and schizophrenia (125, 281). Although there is limited evidence to suggest that glucocorticoid antagonism can improve aspects of cognitive function in bipolar but not schizophrenic patients (125, 434), the actual role of glucocorticoids in the associated health effects of psychiatric disorders is largely untested. Nevertheless, these effects, and the likelihood that abnormal HPA activity indicates inadequately treated disease, remain a concern in psychiatric disorders.

The available evidence that HPA measurements can provide information on the diagnosis, prognosis, or treatment of psychiatric disorders is discussed below. Although assessment of HPA function in OCD and autism has been driven by interest in the role of stress in these disorders (83, 216), current findings in these disorders have been useful more for descriptive purposes than to predict disease course or management. Therefore, this section focuses on depression, anxiety, PTSD, and schizophrenia.

Depression

A “corticosteroid receptor hypothesis” has been formulated to explain the changes in HPA activity during depression and successful treatment (173). This theory posits that brain and possibly corticotroph GR expression or function is defective in depression. Impaired GR-mediated feedback inhibition would account for elevated baseline HPA activity, dexamethasone resistance, and for enhanced production of ACTH-releasing factors that could augment ACTH responses to the combined Dex/CRH test (159, 177). There is post-mortem evidence of reductions in brain GR as well as MR in both unipolar and bipolar depression (251, 269, 311, 437, 444), although it is unclear whether the reductions in corticosteroid receptors are a primary result of the disease or simply reflect down-regulation secondary to disease-associated increases in cortisol (437).

The second part of the corticosteroid receptor hypothesis of depression proposes that the receptor deficits can be reversed with successful treatment. Normalization of DST suppression or ACTH responses to the Dex/CRH test provides functional evidence for treatment effects on glucocorticoid feedback in humans, but quantitative changes in brain corticosteroid receptors after antidepressant treatment have only been able to be studied in animals. Preclinical studies have widely been interpreted to show that antidepressant drugs and electroconvulsive shock treatment increase the function or

expression of GR and MR [reviewed in (173,305)]. Antidepressant effects on GR expression, translocation, and transcriptional activity have been studied in human peripheral blood mononuclear cells (53,154,417), but it is difficult to extrapolate these results to the heterogeneity of GR expression and function in the brain.

Mechanisms by which antidepressants alter HPA activity remain unclear, but have been proposed to include (i) monoamine effects on corticosteroid receptor expression or activity, (ii) changes in glucocorticoid access to the brain, and (iii) changes in downstream signaling pathways engaged by glucocorticoids. All of the monoamines targeted by current antidepressants—serotonin, norepinephrine, and dopamine—have been shown to influence corticosteroid receptor expression or function in animals (60,157,230,233). The effects reported for monoamines on corticosteroid receptor activity are highly dependent on the brain regions studied (158,199,255,256,327), so interpretation of this information awaits better understanding of corticosteroid receptor functions in these regions. Antidepressants have also been reported to control the expression of transport proteins such as multidrug resistance proteins that regulate uptake and retention of many steroids by the brain (445). However, although initial animal studies indicated that antidepressants could increase glucocorticoid access to the brain and thereby facilitate inhibition of HPA activity, subsequent studies have not upheld these findings (266,306). Endocannabinoids, which participate in glucocorticoid feedback regulation of HPA activity (167), have been shown to be increased by common antidepressants in animals (164,165,167). Neurotrophic effects have also been implicated in antidepressant action (23), and antidepressants have been shown to reverse glucocorticoid effects on neurotrophic signaling molecules such as Extracellular Signal-Regulated Kinase (138). Further research is needed to determine the extent to which these intracellular interactions relate to feedback inhibition or other CNS actions of glucocorticoids.

Findings that HPA function often normalizes with improvement or remission of depression have suggested that HPA activity might serve as a state-dependent marker of depression or depression prognosis (159). This conclusion has been difficult to support. Elevated HPA activity is not specific for depression, since it has been observed in other psychiatric conditions [reviewed in (184,338) and above] and in a variety of other diseases including diabetes and stroke (16,338). For the most part, there has been poor correlation between the degree of HPA dysfunction and depression severity, or between the extent of HPA normalization and clinical improvement (5,59,75,88,160,181,229,324,354,399). HPA activity has been also interpreted as a state-dependent marker of depression because abnormalities abate with recovery (16,184,246,324). However, this interpretation is also open to question since aberrant Dex/CRH results have been obtained in people estimated to be at increased risk for depression by virtue of family history, life stress, or personality type, but who are currently healthy (56,106,107).

There has been considerable interest in using baseline HPA measures to predict response to depression treatment. No conclusive generalizations have yet emerged from these analyses (324). Antidepressant response has been correlated both with normal HPA activity on dexamethasone or dex/CRH tests (7,273,308,352) and with elevated HPA activity (190,321,352), including findings that dexamethasone suppression was associated with both monoamine oxidase inhibitor response and resistance (7,190). Other studies have found no correlation between pretreatment HPA activity and antidepressant response (304,344). Since each of the cited studies used a different antidepressant, it is difficult to know if the lack of consensus is due to different medications, differing patient populations, or the unreliability of HPA activity as a marker of antidepressant response.

Perhaps the most robust utility of HPA function tests has been shown for predicting sustained treatment response. Depressed patients who experience psychiatric improvement after treatment but continue to exhibit evidence of elevated HPA activity have consistently been found to be at a higher risk for relapse (36,59,156,295,324,421,464). This information notwithstanding, persistently elevated HPA activity does not indicate how to reduce or avoid this risk of relapse.

The corticosteroid hypothesis of depression is a useful and compelling construct, but it is not without its limitations. As noted above, neither HPA hyperactivity before treatment nor treatment-induced inhibition of HPA activity occurs consistently in depression. Available postmortem data conflict on whether GR are decreased in depression (311,428). Preclinical evidence for antidepressant enhancement of corticosteroid receptor expression or function has also been inconsistent, with a substantial number of studies showing no effect or even inhibitory effects [(161) and references therein]. It is unclear whether these discrepancies are due to differences in drug effects, differences in treatment time, or indirect autoregulatory effects from differences in glucocorticoid secretion.

Some of the discord with the corticosteroid hypothesis in human studies may be attributed to heterogeneity of study populations. Psychotic and bipolar depression have some of the highest rates of HPA hyperactivity (66,119,284,459) and are more likely to exhibit abnormal DST and dex/CRH test results even after successful treatment (156,432,438). It is unclear if these findings reflect the greater likelihood of this population to relapse (38,129,283) or the confounding effects of concurrent medication, such as carbamazepine or lithium, that can increase cortisol levels (5,52,206,223,310,318,433). Comorbid anxiety may also augment HPA activity in depression (456). However, patients with bipolar, manic, or anxious depression have either been included or not explicitly excluded in many studies of depression.

Even patients who respond to antidepressants can be a highly variable population. Antidepressant response, a widely used measure of successful treatment, is defined as a 50% decrease in initial depression score; consequently, patients with higher depression scores before treatment can still be more severely depressed than those with lower initial scores,

even after significant clinical improvement (401). Despite recommendations that remission (typically a score below 7 on the Hamilton Depression Rating Scale) is a more reliable standard (339,400), “response” continues to be equated with treatment success. Thus, lack of antidepressant effects on HPA activity might be attributable to inadequate treatment.

As discussed above, subtypes of depression can also differ in the nature of their HPA dysfunction. There is persuasive [although not unanimous (61,372)] evidence that HPA-related measures are more likely to be low or at least not elevated in atypical depression (15, 131, 135, 455) or in other disorders in which depression is associated with increased sleep and food intake rather than insomnia and reduced appetite (197, 239). Atypical depression has also been distinguished by a better response to monoamine oxidase inhibitor than to tricyclic antidepressants, while melancholic depression responds equally well to both antidepressant classes (387). Since key features and antidepressant responses of melancholic and atypical depression are divergent, inclusion of both subtypes in a study population could obscure changes in HPA activity related to depression and potentially to antidepressant response.

The corticosteroid hypothesis of depression is also limited in focusing solely on GR impairment in depression. As previously discussed, depression can be associated with increased as well as decreased GR sensitivity. Furthermore, glucocorticoids themselves can have potent effects on mood, raising questions as to whether, as proposed by the corticosteroid hypothesis, antidepressant enhancement of GR function is necessarily beneficial. Depression is the most common adverse psychiatric effect of glucocorticoid excess, and has been observed in up to 50% of patients with Cushing’s Syndrome and at least 20% of patients treated with glucocorticoids for anti-inflammatory or immunosuppressive therapy (50, 210, 249, 382). Along these lines, gene polymorphisms in both GR and in the GR-associated FK506 Binding Protein 5 have been associated, albeit not consistently, with unipolar and bipolar depression (177, 380). A polymorphism in the gene for type 1 11 β -hydroxysteroid dehydrogenase, which has the capacity to increase local cortisol levels, has also recently been linked with elevated plasma cortisol and increased depression risk (89). Glucocorticoids can also cause symptoms associated with depression such as mania, anxiety, psychosis, and cognitive deficits (50, 210, 249, 373, 382, 434).

Findings that adrenal steroid synthesis inhibitors and the GR antagonist RU 486 were effective against depression in Cushing’s Syndrome (377, 412, 441) lead to tests of antiglucocorticoid strategies in treatment-resistant depression (377, 412, 441). Several small studies have indicated that the glucocorticoid antagonist RU 486 or glucocorticoid synthesis inhibitors such as ketoconazole and metyrapone could reduce depression symptoms or accelerate antidepressant response in psychotic, bipolar, and unipolar depression (188, 441, 453). The significance of these findings is tempered by the lack of large differences in response rates between antiglucocorticoid- and placebo-treated groups (126, 441) and

by recent negative findings in both psychotic and bipolar depression that may have been due to inadequate drug plasma levels (34, 434). Nevertheless, the potential antidepressant effects of impairing GR signaling indicates that not all GR are impaired in depression, and suggest that the therapeutic actions of antidepressants are unlikely to involve equivalent increases in GR mediating HPA feedback inhibition and GR mediating depressive effects on mood.

Glucocorticoids can also have mood-elevating effects, whose loss might fit better into a model of GR-impaired depression (392). Such effects are manifested in psychiatrically normal subjects as euphoria after exogenous administration, as depression after steroid withdrawal, and in a few cases, as steroid abuse (50, 210, 394). Mood improvements after glucocorticoid treatment occur before significant amelioration of the diseases for which the steroids were prescribed (373, 394), making it unlikely that euphoric effects were due to relief of disease symptoms. Recent findings that glucocorticoids inhibit activity induced by sad images in the subgenual anterior cingulate and ventromedial prefrontal cortex suggest some neuroanatomical substrates for these positive mood effects (392). Consistent with the possibility that inadequate glucocorticoid levels can also predispose to depression, depression rates in Addison’s Disease have been estimated to be approximately twice as high as in the general population (404). Limited but intriguing data indicate that glucocorticoids can improve mood in depression either when given alone (17, 87, 137, 226), or as adjuncts to conventional antidepressants (37, 102). In particular, psychiatric improvement from glucocorticoid supplementation has been found in patients with atypical depression (37). This apparent need for extra glucocorticoids to achieve normal mood in these patients contrasts with their reported greater sensitivity to glucocorticoid feedback (240, 388). These results further underscore the conclusion that GR alterations in depression are more likely to be brain region-specific, rather than global, and that to rectify these deficits, antidepressants would have to have regionally selective, rather than universal, effects on GR function (319).

Nongenomic signaling mechanisms also have the potential to be involved in glucocorticoid effects on mood. Endocannabinoids, which are involved in several brain sites in glucocorticoid feedback inhibition of HPA activity (167), also have mood-elevating effects. Such effects were originally appreciated from positive mood effects of the cannabis plant, but have been reinforced by findings of increased depression in subjects treated with cannabinoid antagonists for body weight control (166). In addition, glucocorticoid inhibition of monoamine reuptake has recently been implicated in the potentiation of cocaine-induced drug-seeking, an animal model of dysphoria-induced relapse in humans (139). It remains to be determined if these nongenomic mechanisms are causally involved in glucocorticoid effects on affective function and if these mechanisms are specific to certain mood symptoms or individual brain regions.

CRH is another HPA factor that has been investigated as a potential mediator of depression. This approach, based

on the initial findings of elevated CSF CRH in depression (25,442), was further justified by findings that central CRH administration evoked depression- and anxiety-like behaviors in animals (22, 153, 174). In addition, polymorphisms of the CRH₁ receptor (CRHR1) gene have been linked with both depression and antidepressant response (153). An initial trial of a CNS-penetrant, nonpeptide CRHR1 antagonist in depression showed promising effects to produce significant improvement in depression and anxiety (463), but lacked placebo controls and was later terminated due to concerns about liver toxicity (224). A second trial with a different nonpeptide CRHR1 antagonist was discontinued because initial analysis of depression scores failed to show significant differences in patient response rates from placebo treatment (33). This termination has been criticized because it is uncertain that the second antagonist achieved adequate levels of receptor blockade (174).

Anxiety disorders

As with depression, elevated HPA activity after treatment correlates with increased risk of relapse in anxiety disorders (1,81). The utility of HPA measures in projecting response to anxiety treatment appears to be as limited as it is for antidepressant response, and may need to be combined with other genetic or environmental susceptibility factors for predictive value (177,235).

Glucocorticoids have also been investigated as potential contributors to anxiety states, but their effects are contradictory. Although much less common than depression or mania, anxiety and panic disorders can occur in patients treated with glucocorticoids for immunosuppressive therapy (32, 50, 210, 322). One study testing the ability of the cortisol synthesis inhibition to reduce carbon dioxide-stimulated anxiety in panic disorder found only marginal effects of metyrapone (29).

On the other hand, there are case reports that glucocorticoid discontinuation can induce panic symptoms (168, 179), and glucocorticoid supplementation has been tested as an aid in anxiety therapy (94). Acute or short-term administration of glucocorticoids has been found, relative to placebo administration, to reduce subjective fear responses to public speaking in social phobia, to viewing spider images in arachnophobia (379), and to height exposure in acrophobia (94). The ability of glucocorticoids to interfere with retrieval of stored, particularly emotional, memories has been proposed to reduce phobic memories, whereas the ability of glucocorticoids to promote consolidation of new memories may reinforce the effects of extinction therapy (94, 379). Low levels of cortisol secretion have been associated with poor responses to behavioral therapy in panic disorder and agoraphobia (371). Like depression, therefore, anxiety may be ameliorated by either attenuating or enhancing glucocorticoid action. The remaining challenge is to identify which individuals might be most responsive to reductions or elevations in glucocorticoids; greater attention to HPA heterogeneity within anxiety disorders (123)

may provide insight into glucocorticoid or other treatment sensitivity.

CRH has also attracted interest as a potential therapeutic target in anxiety. Preclinical evidence is currently more consistent for a role of CRH in anxiety than in depression behaviors (153). CRH expression in the central amygdala, which is both induced by glucocorticoids (259,435) and a stimulus to HPA activity (367,410), can increase anxiety-like behavior (366) and is inhibited by chronic antidepressant or benzodiazepine treatment (163,299). Thus, animal data provide a compelling link between anxiety, CRH, and glucocorticoids. Polymorphism in genes for both CRH (376) and the *CRHR1* gene (243,248) have been associated with anxiety disorders and with faster responses to antidepressant treatment for anxiety. However, despite anxiolytic activity in animals, the CRHR1 antagonist pexacerfont was ineffective in clinical trials of treatments for generalized anxiety disorder (79). Further research will be necessary to target CRH antagonists more specifically to particular patient populations.

Posttraumatic stress disorder

The lower levels of adrenocortical axis activity in PTSD are paradoxical relative to the heightened HPA activity expected both as a consequence of severe stress and as a likely effect of the depression or anxiety that is often comorbid with this disorder (263,450). Since a relatively low percentage of individuals exposed to a life-threatening event go on to develop PTSD, low cortisol levels have been proposed to be a risk factor or susceptibility trait for this disease (447, 450). Consistent with this interpretation, lower cortisol responses to psychological stress have been correlated with higher anxiety levels in several studies of otherwise healthy people (180, 195, 370). Since glucocorticoids attenuate sympathetic activity (147, 227), low glucocorticoid levels could permit excessive sympathetic arousal in PTSD, mimicking an acute stress state (449, 450). Glucocorticoids also interfere with memory retrieval (93), such that inadequate glucocorticoid secretion might allow the return of the intrusive memories that are characteristic of PTSD (450).

Although it has also been suggested that a prior history of trauma may also influence the contribution of low cortisol to PTSD vulnerability (150), longitudinal studies of people who have experienced car accidents, sexual assault, the World Trade Center 9/11 attacks, military service, and major illness or surgery provide support for the theory that low cortisol levels increase the chances of developing PTSD after a life-threatening event (357, 416, 450). Low cortisol levels also predict a poor response to PTSD treatment (451). By analogy with the normalization of elevated HPA activity after successful depression treatment, low HPA activity might be expected to increase with significant reduction or remission in PTSD symptoms, and there is some evidence for such an outcome at least after behavioral therapy (296, 451).

The converse of this theory is that glucocorticoid treatment could help reduce the chances of developing PTSD.

This hypothesis has been upheld in a limited set of trauma survivors treated for 1 month with low cortisol doses (6), accident victims treated with a single iv bolus of cortisol (466), and in intensive care patients, who exhibit similar rates of PTSD as victims of accidents or interpersonal violence (357), that were treated with stress doses of cortisol during their hospital stay. In both a retrospective study of septic shock patients given cortisol to manage hemodynamic stability and in a prospective study of cardiac surgery patients randomized to receive cortisol or placebo specifically to evaluate PTSD risk (357), cortisol treatment significantly reduced PTSD incidence. Both single-dose (198, 466) and extended cortisol administration (6) has been found to reduce PTSD symptoms in trauma or accident victims, indicating that glucocorticoids can attenuate symptoms even after PTSD has developed. The beneficial effects of glucocorticoids, as in anxiety disorders, is thought to be related to the ability of glucocorticoids to inhibit retrieval of intrusive memories or to enhance consolidation of positive memories formed through behavioral therapy (93).

Schizophrenia

It has been argued that HPA activity is involved in the development and expression of schizophrenia (427). This argument has been based on the frequent findings of elevated cortisol in schizophrenia, the ability of antipsychotics to inhibit HPA activity as well as reduce disease symptoms, the capacity of factors that increase susceptibility to schizophrenia, such as stress and drugs of abuse, to increase glucocorticoid release, and the concurrent timing of HPA axis maturation with the typical onset of schizophrenia in adolescence (427). Glucocorticoids can also induce psychosis in Cushing's syndrome and in patients receiving exogenous glucocorticoids for immunosuppressive therapy. As with other psychiatric effects of glucocorticoids, steroid psychosis can occur in individuals with no family or personal history of psychiatric disease, and after unexpectedly low doses or short treatment periods (50, 141, 373, 394, 412, 430, 441).

Plasma cortisol in schizophrenia has been correlated with severity of schizophrenia symptoms under baseline conditions (202, 369, 426, 461) and after serotonergic challenge (244). Elevated cortisol before treatment has also been suggested to be predictive of better antipsychotic response (326). However, as reviewed above, these findings are not universal, and there is limited agreement as to the types of schizophrenia symptoms associated with elevations in glucocorticoids (39). A contributory role for glucocorticoids in the symptomatology of schizophrenia has only been tested so far in a small, short-term study. This study found no effects of a week of treatment with the glucocorticoid antagonist RU 486 on psychiatric condition or cognitive function (125). It remains to be seen whether selecting patients with baseline elevations in cortisol or a longer treatment period might show more definitive effects.

Synthesis and Future Research Needs

Building on theories for the role of glucocorticoids in depression, panic disorder, PTSD, and schizophrenia (93, 320, 355, 427, 434, 441, 450), it is the author's opinion that the diverse and contradictory effects of glucocorticoids on CNS function can provide insight into the relationship between HPA activity and many of the disorders covered here. The ability of glucocorticoids to cause not only depression, anxiety, psychosis, and memory or attention deficits, but also mania, euphoria, and in one case report, obsessive-compulsive behavior (32, 50, 126, 210, 441) in otherwise psychiatrically healthy individuals suggests that there are neural substrates for each glucocorticoid action, and that the effects of glucocorticoids on the CNS must be balanced to permit psychiatric health. Because glucocorticoids regulate both hypothalamic and several extrahypothalamic sources of CRH (259, 435), glucocorticoids could also encompass the roles proposed for CRH in psychiatric disorders. The varied and sometimes opposing effects of glucocorticoids may explain not only the difficulties in establishing clear significance of HPA activity to any given psychiatric disorder but also the weak therapeutic results obtained with glucocorticoid interference, since these strategies would influence the positive mood-elevating and memory-consolidating effects as well as the adverse pro-depressive and memory-impairing effects of glucocorticoids. It is likely that effective glucocorticoid-related treatments will have to target neuron- or region-specific effects of these hormones.

Glucocorticoids are unlikely to be causal agents in all forms of the diseases discussed here, but they provide a compelling connection between alterations in HPA activity and psychiatric symptoms that could aid in treating at least those patients who do exhibit HPA anomalies. In this regard, I have suggested a variation on the corticosteroid receptor hypothesis in depression that could be relevant to any psychiatric disease in which altered HPA activity and glucocorticoid-like changes in mental function occur. I propose that psychiatric disease, or disease vulnerability, can involve abnormally enhanced as well as reduced GR function, that these changes in receptor function or expression are region-specific rather than uniform throughout the brain, and that effective therapies would be expected to have brain region-specific effects on glucocorticoid signaling, to normalize HPA feedback inhibition without accentuating adverse or reducing beneficial effects of glucocorticoids on mood and cognition (319). Supporting the last part of this theory, my laboratory has preclinical evidence for antidepressant-specific effects on GR expression in putative HPA feedback sites that differ from effects on GR expression in the serotonergic and noradrenergic nuclei implicated in mood regulation (161-163). Recently, region-specific alterations in MR have also been predicted and identified post-mortem in depressed patients (269). This modified concept of GR function could account for paradox that glucocorticoid-interference or supplementation strategies respectively seem to benefit depressed patients with melancholic or atypical features (37, 441), whose GR function, as assessed by

dexamethasone suppression, respectively appears to be already impaired or overly sensitive. In the former patients, receptors mediating the depressive effects of glucocorticoids could either be unimpaired or over-stimulated by higher levels of glucocorticoids; in the latter patients, receptors responsible for the mood-elevating effects of glucocorticoids might be either defective or insufficiently activated by low glucocorticoid levels. A similar scenario might be envisioned for some, but probably not all, of the symptoms of panic disorder or schizophrenia, in which glucocorticoids could have a greater impact on brain centers for anxiety and cognitive functions, either because glucocorticoids are elevated or because their CNS targets are more sensitive. The theory that glucocorticoid signaling could be altered only in mood or cognition centers also accommodates the possibility that glucocorticoid interference or supplementation can benefit patients who appear to have normal HPA activity (441).

Matching patient HPA activity to appropriate treatment remains a conundrum. PTSD and atypical depression, the outliers in the search for elevated HPA activity in psychiatric disease, may be the most informative in this regard. Literature available before the advent of the more tolerable SSRIs indicates that PTSD as well as atypical depression responded better to monoamine oxidase inhibitors than to tricyclic antidepressant antidepressants (14, 20, 387, 460). The specific mechanisms for this differential response are unknown, but the acute pharmacology of these drugs indicates that monoamine oxidase inhibitors are more likely than tricyclic antidepressants to increase dopamine (293). It is yet unknown if, by analogy to the normalization of HPA hyperactivity in other forms of depression, clinical response to antidepressants is associated with normalization (i.e., increases in) the lower levels of cortisol often found in these disorders. However, chronic treatment with monoamine oxidase inhibitors can stimulate HPA activity in humans and animals (214, 273, 385), as can sertraline, one of the few antidepressants now approved for PTSD (56, 286, 343). Of interest, sertraline also exhibits the greatest ability of the SSRIs to block dopamine reuptake (286), an action that would also increase extracellular levels of dopamine. Sertraline has also been shown to reduce activity of GRs *in vitro* (448), an action that could translate into higher cortisol levels *in vivo* by impairing glucocorticoid feedback inhibition. Thus, enhancing dopamine transmission could increase HPA activity by interfering with glucocorticoid feedback, ultimately compensating for the relative cortisol deficiency reported in atypical depression or PTSD. A converse relationship of dopamine dysregulation and excess HPA activity has been proposed in schizophrenia and psychotic depression (353, 427).

This speculated mechanism is probably only one of many involved in the beneficial effects of available medications; moreover, the relatively low efficacy of current drugs indicates the need for novel drug targets other than monoamines (288). Nevertheless, identification of medications with reliable effects on the HPA axis would aid in determining if documented HPA hypo- or hyperactivity is useful to predicting

treatment response. Currently, there are limited data to suggest that some antidepressants, benzodiazepines, or antipsychotics may be more effective at inhibiting the HPA axis than others in the same drug class (19, 39, 99, 200, 378). Development of inexpensive tests to evaluate emotional or cognitive sensitivity to glucocorticoids, which is likely to be independent of HPA feedback sensitivity, may also help in identifying treatments for disorders with glucocorticoid-like symptoms.

Depression is recognized to be a heterogeneous disease (66, 288, 400), and it seems reasonable to expect variability in other psychiatric disorders as well. As illustrated by the differences between melancholic and atypical depression, pooling of patients with disparate psychiatric symptoms and HPA features may obscure significant relationships between HPA activity, symptoms, and treatment response. The major challenges ahead are to define the factors accounting for patient heterogeneity and to determine if uniform HPA features within a patient population can predict treatment response. To this end, more careful and detailed characterization of both patients and their HPA function before and after treatment will likely be required.

More uniform reporting of patient characteristics and treatment response definitions will permit more reliable determination of the relationship between HPA measures and treatment. To address the complexity of patient heterogeneity and symptom overlap among disorders, the National Institute of Mental Health has announced new guidelines for clinical research, the Research Domain Criteria [RDoC; (182)], which aim to classify patients based on neural circuit-based behavioral characteristics independent of the diagnostic categories in the Diagnostic and Statistical Manual of Mental Disorders V (DSM-V; (11)). The RDoC also incorporate neural and biological measures (for example, imaging, HPA, or genetic analysis) to determine if treatment response can be better predicted through the intersection of behavior and biomarkers (182).

However, since the NIMH RDoC are currently an experimental approach to diagnosis and treatment, research based on DSM-V classifications can still be made more consistent with greater attention both to current DSM-V subtypes (11) and to unifying or unique features within a study population, both psychiatric and biological, that could identify additional factors influencing treatment response. Such subclassification is not only in the spirit of the NIMH RDoC but would ease transition to the RDoC should this system ultimately be implemented for clinical practice. For example, patients who experience new or worsening psychiatric symptoms during treatment should be tracked. These individuals may not be numerous enough to influence overall group effects, but could provide important insight into clinical and/or HPA features that could be used in future response prediction. If patients with different subtypes are to be studied, the groups should be sufficiently large as to allow statistical analysis of subtype effects. Likewise, as discussed above, medications could confound in interpretation of HPA measurements. Every effort should be made to minimize the number of medications represented and maximize the number of patients on a given

medication so that individual medication effects (including ancillary drugs for symptom management) can be analyzed statistically. As discussed above, defining drug “response” as a 50% reduction in baseline symptoms can still permit considerable variability in treatment outcomes. However, sometimes even this standard is not followed, and response may be claimed if a less than 50% reduction, or even a slight but statistically significant decrease, occurs in baseline scores.

Accurate correlation of changes in HPA activity with treatment response also requires consistent verification of drug administration and drug efficacy. However, such information is not routinely available. Where plasma drug levels are reported, HPA effects have been found to correlate with drug levels more than with changes in clinical scores (34,257,290). Plasma drug and where applicable, dexamethasone levels are, therefore, important to assess patient compliance, dosing adequacy, and pharmacological interactions that could influence response variability, particularly since abnormal corticosteroid metabolism has been reported in depression, schizophrenia, and PTSD (330,384,452).

Accurate assessment of HPA activity further requires appreciation of the sensitivity of this axis to stress, circadian variation, and glucocorticoid inhibition. Ideally, conventions could be derived such that all samples would be collected at the same times in the circadian rhythm, after standardized periods of treatment, and would include basal HPA samples at both the circadian peak (waking) and the circadian nadir (bedtime). Repeated circadian blood samples would be collected remotely from lines extended to a separate room to avoid disturbing subjects. Salivary should be substituted for plasma cortisol measurements wherever appropriate. In pediatric or phobic patients, the extra stress of blood draws could create a “ceiling effect” that confounds effects of psychiatric condition or experimental manipulations on HPA endpoints. Saliva collection tubes with time stamp validation are available to monitor subject compliance. Transparent reporting of raw baseline and stimulus-induced HPA hormone data is necessary to interpret responsiveness of the axis to challenge. Differences in initial cortisol levels can influence responses to subsequent stimuli via feedback inhibition, yet these data are often neglected. Not infrequently only the relative changes in hormones are reported, obscuring whether basal and/or stimulated HPA activity is altered.

HPA physiology is admittedly complex, and it is recognized that these suggestions require extensive resources. Nevertheless, greater attention to these issues will likely improve the use of available resources by providing more consistent results. The contradictions and exceptions, rather than generalizations, may ultimately provide greater insight into the relationship of the HPA axis to psychiatric disease.

Conclusions

Summaries of the points made in this article can be found in Tables 1 and 2. There is evidence, if not unanimous, of aberrant HPA activity in many psychiatric disorders. HPA

activity may be chronically elevated in melancholic depression, bipolar depression, psychotic depression, panic disorder, obsessive-compulsive disorder, and schizophrenia. The HPA axis may be more reactive to stress in social anxiety disorder and autism spectrum disorders. In contrast, HPA activity is more likely to be low in PTSD and atypical depression. Currently, the most reliable use of HPA measures in most disorders is to predict the likelihood of relapse after treatment (1,36,81,223,421,464). However, despite continuing interest in the use of HPA activity as a biomarker to predict treatment response, the unreliable correlation between HPA activity and psychiatric disease has stymied attempts to use HPA measures to choose treatments that would prevent relapse.

Neuropsychiatric treatments can also affect HPA activity, and in some cases these effects have been proposed to contribute to clinical response (319,427,441). Antidepressants are widely considered to inhibit HPA activity, although inhibition is not consistently found in the literature. There is evidence, also uneven, that lithium and carbamazepine have the potential to increase HPA measures, while atypical antipsychotics, and to some extent typical antipsychotics have the potential to inhibit HPA activity. Benzodiazepines have acute inhibitory effects on HPA activity that may dissipate with chronic administration. More systematic comparisons of different drugs, using chronic treatment in healthy as well as psychiatric populations, would be useful to identify medications with intrinsic ability to alter HPA activity. Greater attention to patient heterogeneity and to standardized assessment of HPA function will also aid in determining if defined HPA abnormalities can be used to target psychiatric treatment more effectively.

Table 1 Summary Points: Changes in HPA Activity in Neuropsychiatric Disease

Changes in HPA function are not consistent in any given psychiatric disease and are influenced by patient heterogeneity. With this caveat in mind, the following rough generalizations may be made:

- 1 Depression subtype influences HPA function. Elevated HPA activity and glucocorticoid feedback resistance is most likely to occur in melancholic, bipolar, or psychotic depression, but reduced HPA activity and increased feedback sensitivity is more likely in atypical depression.
- 2 Anxiety disorders exhibit inconsistent increases in HPA activity that are most commonly observed in panic disorder and are probably related to subjective threat perception.
- 3 Posttraumatic stress disorder is primarily associated with reduced HPA activity and greater sensitivity to glucocorticoid feedback; increases in HPA activity may be related to trauma recall.
- 4 Obsessive-compulsive disorder can exhibit increased basal HPA activity with blunted HPA responsiveness to behaviorally provocative stimuli whose significance is unknown.
- 5 Schizophrenia is most commonly associated with increases in HPA activity and reductions glucocorticoid sensitivity, but responses to psychological stress are typically blunted.
- 6 Autism spectrum disorder can be associated with increased HPA activity that is most likely attributable to hyper-reactivity to the stress of blood sampling in pediatric patients.
- 7 The degree of HPA dysfunction does not correlate with disease severity.
- 8 Limited evidence suggests that altered HPA activity can contribute to as well as reflect mood and cognitive disturbances in neuropsychiatric disease.

Table 2 Summary Points: Effects of Chronic Treatment with Psychotropic Medications on HPA Activity

- 1 Antidepressants do not inhibit HPA activity as consistently as often supposed. Discrepant results have been reported with the same drug and may be due to differences in experimental design or patient populations.
- 2 The mood stabilizers lithium and carbamazepine can increase HPA activity.
- 3 Benzodiazepines may not affect HPA activity after chronic treatment, despite inhibitory effects after acute administration.
- 4 Antipsychotics generally inhibit HPA activity, with atypical antipsychotics being slightly more effective than typical antipsychotics in this regard.
- 5 Persistently abnormal HPA activity after treatment correlates with a poorer or less sustained treatment response.

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