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# Stress and the brain

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**Abstract**

Stress is a risk factor for a variety of illnesses, involving the same hormones that ensure survival during a period of stress. Although there is a considerable ambiguity in the definition of stress, a useful operational definition is: "anything that induces increased secretion of glucocorticoids".

The brain is a major target for glucocorticoids. Whereas the precise mechanism of glucocorticoid-induced brain damage is not yet understood, treatment strategies aimed at regulating abnormal levels of glucocorticoids, are worth examining.


*Keywords:* Stress; Glucocorticoids; HPA system; CRH secretion; PTSD

## 1. Stress, stressors, stressed-out

Over the past decades, rapid progress has been made in elucidating the effects of hormones on brain development, normal brain functioning, aging of the brain and brain diseases. This field of research, which originally has been labeled "psychoneuro-endocrinology", is rapidly expanding and one of its most interesting topics is the impact of stress on the brain. Stress is a risk factor for a variety of illnesses, ranging from metabolic and cardiovascular disorders to mental illness. The pathways by which stressful events can promote the development of such divergent forms of illness involve the same hormones that ensure survival during a period of stress [63]. Although stress is a widely used word and an important aspect of our daily lives and conversations, there is considerable ambiguity in its definition. Generally stress is defined as responses to severe demands on the body [87]. While the late Hans Selye, the pioneer of stress research, has emphasized physical stressors, psychological and experimental factors are among the most powerful stressors for human beings. Therefore, a definition of stress more focused on the central nervous system consists in the view of stress as alterations in psychological homeostatic processes [12]. Such stressful events, or stressors, could consist, e.g. in novelty, withholding of reward, and anticipation of punishment rather than the punishment itself [62]. However, a widely agreed-upon and more operational definition of stress is "anything that induces increased secretion of glucocorticoids" [53].

The brain is the master controller of the interpretation of what is stressful and of the behavioral and physiological responses that are produced. While a brief period of controllable stress may be harmless for physical or mental health, a lack of control and uncertainty can produce a chronic state of distress that is believed to enhance vulnerability to stress-related disorders.

The stress system coordinates the adaptive response of the organism to real or perceived stressors. The main components of the stress system are the hypothalamic–pituitary–adrenal (HPA) loop and the limbs of the locus ceruleus-norepinephrine/autonomic (LC/NE) pathways. The action of these two systems appears to be synergistic. Whereas catecholamines facilitate the availability of energy to vital organs, glucocorticoids from the adrenals function as "antistress" hormones, helping to contain or shut down the neural defensive reactions that have been initiated by stress [60,71]. While the adaptive responses are the short activation of the HPA system, the maladaptive responses often result from the overproduction of stress hormones and/or the failure of termination of the HPA activation. Chronic stress can result in sustained increases in glucocorticoids, in case of humans, cortisol. However, depending on the nature of the stressor, the HPA system may also become tonically inhibited due to a chronic adaptation to the stressor. Thus, in classic stress theory, stressors that result in the activation of CRH release from

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paraventricular neurons in the hypothalamus also result in elevated glucocorticoid (GC) levels, whereas lower levels of GC are thought to result directly from a cessation of activation by CRH.

Importantly, the overall activity of the HPA system is regulated by the hippocampus through its binary glucocorticoid receptors system.

## 2. The hormonal stress response

When humans experience psychological or physical stress, parvocellular neurons of the paraventricular hypothalamus (PVN) produce increased amounts of CRH and vasopressin (VP), which are released into portal vessels activating secretion of corticotropin (ACTH) from the corticotrophs of the anterior pituitary cells. ACTH itself enters the circulating blood and stimulates the secretion of glucocorticoids (cortisol in humans and corticosterone in rats) from the cortex of the adrenal glands (for review see [19]). The secretion of the end product of the HPA system, glucocorticoids, is kept within an 'optimal' time-integrated narrow range by inhibition of its own release by means of negative feedback through corticosteroid-receptors [71]. Following stress-induced CRH secretion, a 'compensatory' increase in CRH mRNA expression in PVN has been observed in the mature [54] as well as the developing rat [109]. Evidently glucocorticoids suppress this compensatory enhancement of CRH mRNA expression in PVN to shut down the stress response and return the individual to homeostasis [95,110,111]. The mechanism of this glucocorticoid-induced down-regulation of CRH levels primarily involves activation of glucocorticoid receptors in PVN [95]. In addition, glucocorticoids can bind their cognate receptors in the hippocampus to activate indirect pathways leading to suppression of hypothalamic CRH mRNA expression [4,34]. Although increased glucocorticoid secretion is critical to the adaptation of an organism to stress, prolonged or excessive exposure to glucocorticoids may be deleterious because of untoward effects on the CNS and other organs [60].

The effect of CRH is not limited to its role as a hypothalamic hypophysiotropic hormone, rather it also serves as a neurotransmitter within the CNS, mediating autonomic and behavioral stress responses. When administered directly into the CNS of laboratory animals, CRH produces effects that are reminiscent of stress, depression, and anxiety, including increases in peripheral catecholamine secretion, heart rate and arterial pressure, decreased appetite, disruption of sleep, facilitation of fear conditioning and more [74]. The amygdaloid CRH activation of the noradrenergic neurons of the locus coerulus seems to be critical for the expression of behavioral responses to stress [5,73,84,101]. These effects are mediated via binding of CRH to $CRH_1$ receptors, whereas $CRH_2$ receptors that bind with high affinity to urocortin, a related endogenous neuropeptide, appear to be involved in dampening stress and fear [2] although their role is less clear [96,97].

Glucocorticoids apparently can restrain one set of CRH producing cells, namely the system linked to HPA function, while initiating amygdala production of CRH for fear-related behaviors [83].

## 3. Stress, glucocorticoid receptors and the hippocampus

One of the most important brain areas that regulates stress response and is at the same time affected by stress responses is the hippocampus. The hippocampus has a rich concentration of glucocorticoid receptors including type I (mineralocorticoid) and type II (glucocorticoid). Type II receptors have a lower affinity for glucocorticoids than type I receptors and they play a more important role in modulation of HPA functions during high release of glucocorticoids as is seen during acute stress [99] whereas type I receptors regulate the basal activity of the HPA system. Also, the hippocampus modulates glucocorticoid release through inhibitory effects on the HPA system. These findings indicate that the hippocampus has an important role in integrating neurohumoral, and neurochemical responses to stress. Glucocorticoids appear to have a wide range of effects on this brain area, which is also of major importance for cognitive functions such as information processing. It has been shown that normal GC concentrations are essential for proper synaptic transmission and the maintenance of neuronal viability of the different hippocampal subfields.

However, there is now ample evidence that chronic elevation of corticosteroid levels leads to neurodegeneration or suppressed neurogenesis in the hippocampus [20,82]. Direct glucocorticoid exposure results in decreased dendritic branching [27,105], alterations in synaptic terminal structure [56], a loss of neurons [100], and an inhibition of neuronal regeneration in the dentate gyrus [27]. These effects of glucocorticoids are exerted through disruption of cellular metabolism [50] and by increasing the vulnerability of hippocampal neurons to a variety of insults, including endogenously released excitatory amino acids [3,81,103] (for review see [80]). At the other extreme, depletion of corticosterone could induce apoptosis in granule cells of the dentate gyrus [43,90,91].

The structural changes of hippocampal neurons after chronic absence or chronic overexposure to corticosteroids indicate that steroid-dependent expression of genes is of crucial importance for hippocampal integrity.

These findings are of importance for several neuropsychiatric diseases, especially depression and posttraumatic stress disorder [80]. Several studies found a significant reduction in hippocampal volume in depressed patients [10,88,89]. Interestingly, a recent study has shown that in primates psychological stress reduces the proliferation of new cells in the hippocampus, causing a decrease of neuronal function

and viability and was associated with a trend towards a decrease in total hippocampal volume. However, the treatment of these animals with the antidepressant tianeptine prevented these stress-induced changes [18]. This result could be in line with previous reports of an increase of corticosteroid-receptor concentration through antidepressants that render the HPA system more susceptible to feedback inhibition by GC [6].

Another disease with potentially stress-induced hippocampal damage is posttraumatic stress disorder (PTSD), where studies have found a reduction in hippocampal volume following combat trauma or childhood abuse [9,28,93].

## 4. Glucocorticoid receptors and HPA system regulation

The ability of the glucocorticoid negative feedback system to limit the production of GC during stress can be impaired by early life stress, history of chronic emotional/physical stress and older age [30,35,49,102]. A nonstressed HPA system is characterized by an increased variance mostly due to a wide circadian variation, with distant morning zeniths and evening nadirs, a discrete but small lunch-induced GC peak and an appropriate suppression of the afternoon GC concentrations in response to low-dose dexamethason.

A chronically stressed HPA system and that of older individuals on the other hand, is characterized by a decreased variance mostly due to evening nadir elevations and morning zenith decreases, a large lunch-induced GC response and an inadequate suppression of afternoon GC levels after overnight dexamethason [26]. These findings suggest chronic hypersecretion of CRH in elderly and in chronically stressed individuals and a failed reset of their HPA system [16]. In the presence of a properly functioning glucocorticoid negative feedback system, GC secretion would be minimized to the greatest possible extent. This is why GC levels are not necessarily indicative of a chronically stressed HPA system.

The HPA response to stress is highly dependent on specific psychological factors such as control and predictability. Also, there is evidence that the anticipation of an event is as potent an activator of the HPA system as the event itself, e.g. phobic patients show the highest elevation of cortisol on the day prior to being exposed to the phobic stimuli [106].

## 5. Stress allostasis and aging

Allostasis was introduced to refer to the process of re-establishing homeostasis in the face of challenge [62]. The term means achieving stability through change and refers in part to the process of increasing sympathetic and HPA activity to promote adaptation and to re-establish homeostasis. Allostasis also highlights our ability to anticipate, adapt or cope with impeding future events [84]. When allostatic systems remain active they can cause wear and tear on tissues and accelerate pathophysiology—a phenomenon that is called allostatic load [61]. Examples of allostatic load include loss of bone mass in depression associated with elevated levels of glucocorticoids [70,85,86] and atrophy of neurons in the hippocampus as a result of recurrent, hypercortisolemic depression [89].

One of the most insidious features of chronic stress, and possibly older age, is that it tends to enhance the magnitude to responses to subsequent presentations of either the same or novel stressors [46]. This sensitization also applies to HPA system responses since chronic stress has been found to induce a sensitization of the HPA system that is not identifiable under “resting” conditions but becomes evident with the imposition of a novel acute stressor [31]. Recent animal research suggests that by increasing CRH gene expression in the central nucleus of the amygdala (and bed nucleus of the stria terminalis), glucocorticoids increased the likelihood that events would be perceived as fearful and the individual be overwhelmed by anticipatory fear [83]. It has been suggested that such an allostatic regulation is also anticipatory and therefore without clear set point boundaries, and thus not simply reactive to homeostatic imbalances.

Thus, the inability to restrain central CRH and systemic glucocorticoids in stressed or aged subjects may be a paradigmatic example of allostatic load.

## 6. Stress earlier in life and its impact on future health: anxiety disorders and PTSD

Although a vast amount of clinical and experimental evidence demonstrates that early life experiences influence health and reproductivity in later life and may sensitize the young to stressors elevating the risk for stress-induced psychopathology, the precise mechanism of this influence is not clearly understood. Recent research has provided evidence that the prolonged or exaggerated response to stress through the repeated, severe activations of the HPA system has profound effects on physiological and cognitive functions, e.g. GCs act on the hippocampus and amygdala to disrupt episodic memory [62]. During development, proper function of both the activation and the ‘shut-off’ mechanisms of the HPA loop is critical to permit coping with acute stress, but also to allow normal growth and maturational processes which may be adversely influenced by high levels of GCs [45,52,98]. Early maternal separation or handling of neonatal rats can program widespread and lifelong changes in various transmitter systems that regulate the stress systems. Research by the group of Michael Meany has shown interesting results regarding the conditions of rearing and adult stress regulation. High level of maternal licking/grooming and arched-back nursing correlates with reduced CRH mRNA expression and enhanced glucocorticoid negative feedback, and lower stress responses in the adult [14].

Early stimulation of neonatal rats (e.g. handling) affects their endocrine and behavioral responses later in life. They show increased exploration, less anxiety in an open field, a reduced taste neophobia and conditioned taste aversion [17]. In addition to the behavioral changes, these animals acquired an altered activity of the HPA system. Handled rats had higher levels of glucocorticoids immediately after shock exposure, but a more rapid return to basal levels. In contrast, nonhandled rats had a much slower rise in the post shock secretion of glucocorticoids [69]. These results are in line with the finding that handling causes an increased number of glucocorticoid receptor expressions in the hippocampus [66,67]. Furthermore, CRH mRNA and protein levels, under basal conditions, are significantly higher in nonhandled rats than in handled ones and the CRH release in response to stress is greater in nonhandled rats compared with handled rats [75]. Finally, handled animals show more modest stress-induced suppression of the immune function [8] and age-related increases in basal and stress-induced HPA activity is significantly less apparent in handled animals. Also, these animals have less neuropathological and behavioral evidence of brain aging [65].

These results of animal research are pertinent to human studies since the relationship between early life events and health in adulthood, which is well known from clinical studies, appears to be, in part, mediated by parental influences on the development of neural systems that underlie the expression of behavioral and endocrine responses to stress [24,25,32]. As adults, victims of childhood physical or sexual abuse are at a considerably greater risk for mental illness, as well as for obesity, diabetes, and heart disease [11,23,59]. Even when children are not physically or psychologically abused, persistent emotional neglect, family conflict or harsh, inconsistent discipline increases the risk for depression and anxiety disorders [38,39] as well as obesity [55,79]. Even prenatal stress has been related to an increased risk for major depression in adulthood [44]. As for now only animal research data suggest that early trauma may persistently weaken corticosteroid signaling, leading to disinhibited release of CRH, ACTH, and corticosteroids which, in turn, may have behavioral sequelae that are related to a number of depressive symptoms. These data might be extrapolated to the human situation, explaining why individuals who where abused during childhood may be more likely to develop depression in later life [33].

Research in the last decade has shown that early life stress constitutes a major risk for PTSD as well [33]. In adult PTSD, it is hypothesized that the catecholamine- and HPA-system responses to stress become maladaptive, causing long-term negative consequences [108]. This holds true for sexual and/or physical abuse in early childhood as well as for experience of trauma (e.g. combat experience) later in life [33].

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Several studies have consistently found low cortisol concentrations together with high CRH levels and dexamethasone “supersuppression” in the dexamethason-suppression test (DST) in patients with PTSD suggesting an enhanced negative feedback inhibition of cortisol in this disorder [108]. This “sensitization” of the HPA system is consistent with the clinical presentation of PTSD, where patients typically show an unusually heightened response to stress and symptoms of increased startle, hypervigilance, and physiological arousal. In contrast, others have reported an increased HPA axis activity in PTSD [51,77].

It is still not understood if low cortisol levels are an antecedent, that is, a risk factor for PTSD, or the consequence, that is a result of the disease process. A recent study points towards high cortisol levels at the onset of PTSD and subsequently low cortisol levels [1]. However, the fact that a significant number of trauma survivors show low cortisol levels is counterintuitive to the idea that stress (and psychiatric symptoms) would be associated with high cortisol. Since cortisol in PTSD is generally obtained at least several months after exposure to the stressor, these low levels may rather reflect a chronic adaptation of the HPA system. However, two studies have demonstrated a low cortisol response to acute trauma in patients who subsequently developed PTSD after retraumatization [64,78].

## 7. Stress and depression

The preclinical literature supports the premise that excess CRH within the CNS may evoke a depressive symptom complex consisting of loss of appetite, insomnia and intense anxiety. Numerous clinical studies also suggest that hyperactivity of central CRH neuronal activity may be involved in the pathophysiology of depressive disorders [36]. In particular, the hypercortisolemia and impaired negative feedback of cortisol on the HPA system observed in melancholic depression have been attributed to a primary central CRH hyperdrive [37]. These changes in HPA system regulation were observed, e.g. by the means of the DST which shows a nonsuppression of cortisol following administration of the synthetic glucocorticoid dexamethasone [13]. Later, researchers employed the combined dexamethasone suppression/CRH stimulation test (DEX/CRH-test) which showed paradoxically increased ACTH and cortisol secretion after CRH infusion in dexamethasone-pretreated patients (for review see [35,42,47]). About 50% of patients suffering from depression have a hyperactive HPA system resulting in hypercortisolism [15]. In these patients CRH and VP expression in PVN may be enhanced, the adrenals show hypertrophy, and basal corticosteroid levels are elevated [76].

The reason for HPA hyperactivity and for enhanced synthesis and release of CRH in depression is not yet clear, genetic and experience-related factors may interact to induce these manifold changes [20]. Sapolsky [80] speculated that the dexamethasone resistance present in many depressed patients may result from a transient down-regulation of glucocorticoid receptors in the hippocampus, the central regulator of the activity of the HPA system. Interestingly, preliminary evidence suggests that feedback resistance and mild hypercortisolism are already present in healthy subjects at genetic risk for depression [40].

Standard antidepressants, known to affect mainly catecholaminergic and serotonergic neurotransmission, seem to act also through normalization of initial HPA dysregulation. The time course of these neuroendocrine actions on HPA activity and, more specifically, on hippocampal corticosteroid receptors, follows closely that of clinical improvement, and supports the hypothesis that there is a causal link between HPA activity and antidepressant effect [41]. Finally, several studies have reported the improvement of depressive symptoms through steroid suppression in depressed patients and patients suffering from Cushing's disease [72,107].

## 8. Stress, HPA system and addiction

Early family adversity, including abuse, emotional neglect, and harsh, inconsistent punishment is a risk factor for drug abuse [113]. Animals reared under conditions of prolonged maternal separation showed decreased dopamine transporter binding in the nucleus accumbens, increased dopamine release in response to acute stress, and enhanced behavioral sensitivity to cocaine [68].

Cross-sensitization occurs between stress and drugs and repeated exposure to stress enhances behavioral responses not only to subsequent stress but also to drugs of abuse [92,94]. This behavioral sensitization to stress and drugs is associated with augmented dopamine release in the nucleus accumbens [22,46]. Animal studies demonstrated that the dopaminergic transmission in the nucleus accumbens is facilitated by glucocorticoids [7,57] and that glucocorticoid treatment enhances amphetamine-consumption [21,58]. Repeated exposure to stress or to psychostimulant drugs produces a sensitization of mesolimbic dopaminergic neurons. Predictably, HPA system status also influences responses to psychostimulants. Therefore, stress and/or glucocorticoids seem to facilitate under certain conditions the abuse of drugs.

## 9. CRH antagonists for treatment of depression and other stress-related disorders

There are promising novel drugs that may be efficient in the treatment of stress-related disorders. Given the integral role of CRH and its receptors in the mediation of stress and emotion, the CRH receptor antagonists are being discussed as novel antidepressants and anxiolytics as well as potentially preventive treatments, e.g. PTSD.

This concept is even more intriguing since, as shown above, research has found substantial alterations in central CRH systems brought about by early life stress. Oral administration of the CRH receptor antagonist antalarmin significantly decreased cerebrospinal fluid concentration of CRH, and pituitary–adrenal and autonomic responses to stress as well as inhibiting behaviors indicative of fear and anxiety in adult primates [29]. In rats exposed to prenatal stress the treatment with CRH antagonists reversed the characteristic increases of fearful behavior observed in these animals [104]. In rat pups, the CRH antagonist CP 154,526 diminished vocalization indicative of anxiety in response to separation from litters [48]. The research group of Florian Holsboer of the Max-Planck-Institute of Psychiatry has recently proven the antidepressant and anxiolytic properties of the selective CRH receptor antagonist R121919 in a clinical trial of depressed patients [112].

## 10. Conclusion

The brain is a major target for glucocorticoid hormones by which psychological and physical disorders could be caused. While further study is certainly necessary to understand the precise mechanisms of glucocorticoid-induced brain endangerment, treatment strategies aimed at regulating abnormal levels of glucocorticoids are currently worth examining.

Vulnerability to stress and disease is surely not the exclusive consequence of an adverse early environment, but is highly impacted by genetic factors [25]. The concatenation of genetics, early life stress, and ongoing stress may ultimately determine individual stress responsiveness and the manifestation of psychiatric disorders.

## References

[1] Aardal-Eriksson E, Eriksson TE, Holm AC, Lundin T. Salivary cortisol and serum prolactin in relation to stress rating scales in a group of rescue workers. Biol Psychiatr 1999;46:850–5.
[2] Arborelius L, Owens MJ, Plotsky PM, Nemeroff CB. The role of corticotropin-releasing factor in depression and anxiety disorders. J Endocrinol 1999;160:1–12.
[3] Armanini MP, Hutchins C, Stein BA, Sapolsky RM. Glucocorticoid endangerment of hippocampal neurons is NMDA-receptor dependent. Brain Res 1990;532:7–12.
[4] Avishai-Eliner S, Eghbal-Ahmadi M, Tabachnik E, Brunson KL, Baram TZ. Down-regulation of hypothalamic corticotropin-releasing hormone messenger ribonucleic acid (mRNA) precedes early-life experience-induced changes in hippocampal glucocorticoid receptor mRNA. Endocrinology 2001;142:89–97.
[5] Bakshi VP, Shelton SE, Kalin NH. Neurobiological correlates of defensive behaviors. Prog Brain Res 2000;122:105–15.
[6] Barden N, Reul JM, Holsboer F. Do antidepressants stabilize mood through actions on the hypothalamic–pituitary–adrenocortical system? Trends Neurosci 1995;18:6–11.
[7] Barrot M, Marinelli M, Abrous DN, Rouge-Pont F, Le Moal M, Piazza PV. The dopaminergic hyper-responsiveness of the shell

of the nucleus accumbens is hormone-dependent. Eur J Neurosci 2000;12:973–9.
[8] Bhatnagar S, Shanks N, Meaney MJ. Plaque-forming cell responses and antibody titers following injection of sheep red blood cells in nonstressed, acute, and/or chronically stressed handled and nonhandled animals. Dev Psychobiol 1996;29:171–81.
[9] Bremner JD, Randall P, Scott TM, Bronen RA, Seibyl JP, Southwick SM, et al. MRI-based measurement of hippocampal volume in patients with combat-related posttraumatic stress disorder. Am J Psychiatr 1995;152:973–81.
[10] Bremner JD, Narayan M, Anderson ER, Staib LH, Miller HL, Charney DS. Hippocampal volume reduction in major depression. Am J Psychiatr 2000;157:115–8.
[11] Brown GR, Anderson B. Psychiatric morbidity in adult inpatients with childhood histories of sexual and physical abuse. Am J Psychiatr 1991;148:55–61.
[12] Burchfield SR. The stress response: a new perspective. Psychosom Med 1979;41:661–72.
[13] Caroll BJ, Feinberg M, Greden JF, Tarika J, Albala AA, Haskett RF, et al. A specific laboratory test for the diagnosis of melancholia. Standardization, validation, and clinical utility. Arch Gen Psychiatr 1981;38:15–22.
[14] Champagne F, Meaney MJ. Like mother, like daughter: evidence for non-genomic transmission of parental behavior and stress responsivity. Prog Brain Res 2001;133:287–302.
[15] Checkley S. The neuroendocrinology of depression and chronic stress. Br Med Bull 1996;52:597–617.
[16] Chrousos GP. The role of stress and the hypothalamic–pituitary–adrenal axis in the pathogenesis of the metabolic syndrome: neuro-endocrine and target tissue-related causes. Int J Relat Metab Disord 2000;24(Suppl 2):S50–5.
[17] Cirulli F. Role of environmental factors on brain development and nerve growth factor expression. Physiol Behav 2001;73:321–30.
[18] Czeh B, Michaelis T, Watanabe T, Frahm J, de Biurrun G, van Kampen M, et al. Stress-induced changes in cerebral metabolites, hippocampal volume, and cell proliferation are prevented by antidepressant treatment with tianeptine. Proc Natl Acad Sci USA 2001;98:12796–801.
[19] De Bellis MD, Baum AS, Birmaher B, Keshavan MS, Eccard CH, Boring AM, et al. A.E. Bennett Research Award. Developmental traumatology. Part I: Biological stress systems. Biol Psychiatr 1999;45:1259–70.
[20] de Kloet ER, Vreugdenhil E, Oitzl MS, Joels M. Brain corticosteroid receptor balance in health and disease. Endocr Rev 1998;19:269–301.
[21] Deroche V, Marinelli M, Le Moal M, Piazza PV. Glucocorticoids and behavioral effects of psychostimulants. II: Cocaine intravenous self-administration and reinstatement depend on glucocorticoid levels. J Pharmacol Exp Ther 1997;281:1401–7.
[22] Doherty MD, Gratton A. High-speed chronoamperometric measurements of mesolimbic and nigrostriatal dopamine release associated with repeated daily stress. Brain Res 1992;586:295–302.
[23] Felitti VJ, Anda RF, Nordenberg D, Williamson DF, Spitz AM, Edwards V, et al. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study. Am J Prev Med 1998;14:245–58.
[24] Francis DD, Meaney MJ. Maternal care and the development of stress responses. Curr Opin Neurobiol 1999;9:128–34.
[25] Francis DD, Caldji C, Champagne F, Plotsky PM, Meaney MJ. The role of corticotropin-releasing factor—norepinephrine systems in mediating the effects of early experience on the development of behavioral and endocrine responses to stress. Biol Psychiatr 1999;46:1153–66.
[26] Gotthardt U, Schweiger U, Fahrenberg J, Lauer C, Holsboer F, Heuser I. Cortisol, ACTH, and cardiovascular response to a cognitive challenge paradigm in aging and depression. Am J Physiol 1995;268:R865–73.
[27] Gould E, Woolley CS, McEwen BS. Short-term glucocorticoid manipulations affect neuronal morphology and survival in the adult dentate gyrus. Neuroscience 1990;37:367–75.
[28] Gurvits TV, Shenton ME, Hokama H, Ohta H, Lasko NB, Gilbertson MW, et al. Magnetic resonance imaging study of hippocampal volume in chronic, combat-related posttraumatic stress disorder. Biol Psychiatr 1996;40:1091–9.
[29] Habib KE, Weld KP, Rice KC, Pushkas J, Champoux M, Listwak S, et al. Oral administration of a corticotropin-releasing hormone receptor antagonist significantly attenuates behavioral, neuroendocrine, and autonomic responses to stress in primates. Proc Natl Acad Sci USA 2000;97:6079–84.
[30] Halbreich U, Asnis GM, Zumoff B, Nathan RS, Shindledecker R. Effect of age and sex on cortisol secretion in depressives and normals. Psychiatr Res 1984;13:221–9.
[31] Hauger RL, Lorang M, Irwin M, Aguilera G. CRH receptor regulation and sensitization of ACTH responses to acute ether stress during chronic intermittent immobilization stress. Brain Res 1990;532:34–40.
[32] Heim C, Owens MJ, Plotsky PM, Nemeroff CB. The role of early adverse life events in the etiology of depression and posttraumatic stress disorder. Focus on corticotropin-releasing factor. Ann NY Acad Sci 1997;821:194–207.
[33] Heim C, Nemeroff CB. The role of childhood trauma in the neurobiology of mood and anxiety disorders: preclinical and clinical studies. Biol Psychiatr 2001;49:1023–39.
[34] Herman JP, Schafer MK, Young EA, Thompson R, Douglass J, Akil H, et al. Evidence for hippocampal regulation of neuroendocrine neurons of the hypothalamo–pituitary–adrenocortical axis. J Neurosci 1989;9:3072–82.
[35] Heuser I, Yassouridis A, Holsboer F. The combined dexamethasone/CRH test: a refined laboratory test for psychiatric disorders. J Psychiatr Res 1994;28:341–56.
[36] Heuser I, Schweiger U, Gotthardt U, Schmider J, Lammers C-H, Dettling M, et al. Pituitary–adrenal-system regulation and psychopathology during amitriptyline treatment in elderly depressed patients and in normal controls. Am J Psychiatr 1996;153:93–9.
[37] Heuser I, Bissette G, Dettling M, Schweiger U, Gotthardt U, Schmider J, et al. Cerebrospinal fluid concentrations of corticotropin-releasing hormone, vasopressin, and somatostatin in depressed patients and healthy controls: response to amitriptyline treatment. Depress Anxiety 1998;8:71–9.
[38] Holmes SJ, Robins LN. The influence of childhood disciplinary experience on the development of alcoholism and depression. J Child Psychol Psychiatr 1987;28:399–415.
[39] Holmes SJ, Robins LN. The role of parental disciplinary practices in the development of depression and alcoholism. Psychiatr 1988;51:24–36.
[40] Holsboer F, Lauer CJ, Schreiber W, Krieg JC. Altered hypothalamic–pituitary–adrenocortical regulation in healthy subjects at high familial risk for affective disorders. Neuroendocrinology 1995;62:340–7.
[41] Holsboer F, Barden N. Antidepressants and hypothalamic–pituitary–adrenocortical regulation. Endocr Rev 1996;17:187–205.
[42] Holsboer F. The corticosteroid receptor hypothesis of depression. Neuropsychopharmacology 2000;23:477–501.
[43] Hornsby CD, Grootendorst J, de Kloet ER. Dexamethason does not prevent seven-day ADX-induced apoptosis in the dentate gyrus of the rat hippocampus. Stress 1996;1:51–64.
[44] Hulshoff Pol HE, Hoek HW, Susser E, Brown AS, Dingemans A, Schnack HG, et al. Prenatal exposure to famine and brain morphology in schizophrenia. Am J Psychiatr 2000;157:1170–2.
[45] Kalin NH, Shelton SE, Davidson RJ, Kelley AE. The primate amygdala mediates acute fear but not the behavioral and physiological components of anxious temperament. J Neurosci 2001;6:2067–74.
[46] Kalivas PW, Stewart J. Dopamine transmission in the initiation and expression of drug- and stress-induced sensitization of motor activity. Brain Res Brain Res Rev 1991;16:223–44.

[47] Keck ME, Holsboer F. Hyperactivity of CRH neuronal circuits as a target for therapeutic interventions in affective disorders. Peptides 2001;22:835–44.
[48] Kehne JH, Coverdale S, McCloskey TC, Hoffman DC, Cassella JV. Effects of the CRH(1) receptor antagonist, CP 154,526, in the separation-induced vocalization anxiolytic test in rat pups. Neuropharmacology 2000;39:1357–67.
[49] Kling MA, Roy A, Doran AR, Calabrese JR, Rubinow DR, Whitfield Jr HJ, et al. Cerebrospinal fluid immunoreactive corticotropin-releasing hormone and adrenocorticotropin secretion in Cushing's disease and major depression: potential clinical implications. J Clin Endocrinol Metab 1991;72:260–71.
[50] Lawrence MS, Sapolsky RM. Glucocorticoids accelerate ATP loss following metabolic insults in cultured hippocampal neurons. Brain Res 1994;646:303–6.
[51] Lemieux AM, Coe CL. Abuse-related posttraumatic stress disorder: evidence for chronic neuroendocrine activation in women. Psychosom Med 1995;57:105–15.
[52] Levine S. The pituitary–adrenal system and the developing brain. Prog Brain Res 1970;32:79–85.
[53] Levine S. Influence of psychological variables on the activity of the hypothalamic–pituitary–adrenal axis. Eur J Pharmacol 2000;405:149–60.
[54] Lightman SL, Young III WS. Influence of steroids on the hypothalamic corticotropin-releasing factor and preproenkephalin mRNA responses to stress. Proc Natl Acad Sci USA 1989;86:4306–10.
[55] Lissau I, Sorensen TI. Parental neglect during childhood and increased risk of obesity in young adulthood. Lancet 1994;343:324–7.
[56] Magarinos AM, Verdugo JM, McEwen BS. Chronic stress alters synaptic terminal structure in hippocampus. Proc Natl Acad Sci USA 1997;94:14002–8.
[57] Marinelli M, Aouizerate B, Barrot M, Le Moal M, Piazza PV. Dopamine-dependent responses to morphine depend on glucocorticoid receptors. Proc Natl Acad Sci USA 1998;95:7742–7.
[58] Marinelli M, Rouge-Pont F, Deroche V, Barrot M, Jesus-Oliveira C, Le Moal M, et al. Glucocorticoids and behavioral effects of psychostimulants. I: Locomotor response to cocaine depends on basal levels of glucocorticoids. J Pharmacol Exp Ther 1997;281:1392–400.
[59] McCauley J, Kern DE, Kolodner K, Dill L, Schroeder AF, DeChant HK, et al. Clinical characteristics of women with a history of childhood abuse: unhealed wounds. JAMA 1997;277:1362–8.
[60] McEwen BS. Protective and damaging effects of stress mediators. N Engl J Med 1998;338:171–9.
[61] McEwen BS. Stress, adaptation, and disease. Allostasis and allostatic load. Ann NY Acad Sci 1998;840:33–44.
[62] McEwen BS. The neurobiology of stress: from serendipity to clinical relevance. Brain Res 2000;886:172–89.
[63] McEwen BS, Stellar E. Stress and the individual. Mechanisms leading to disease. Arch Intern Med 1993;153:2093–101.
[64] McFarlane AC, Atchison M, Yehuda R. The acute stress response following motor vehicle accidents and its relation to PTSD. Ann NY Acad Sci 1997;821:437–41.
[65] Meaney MJ. Maternal care, gene expression, and the transmission of individual differences in stress reactivity across generations. Annu Rev Neurosci 2001;24:1161–92.
[66] Meaney MJ, Aitken DH, Viau V, Sharma S, Sarrieau A. Neonatal handling alters adrenocortical negative feedback sensitivity and hippocampal type II glucocorticoid receptor binding in the rat. Neuroendocrinology 1989;50:597–604.
[67] Meaney MJ, Bhatnagar S, Diorio J, Larocque S, Francis D, O'Donnell D, et al. Molecular basis for the development of individual differences in the hypothalamic–pituitary–adrenal stress response. Cell Mol Neurobiol 1993;13:321–47.
[68] Meaney MJ, Brake W, Gratton A. Environmental regulation of the development of mesolimbic dopamine systems: a neurobiological mechanism for vulnerability to drug abuse? Psychoneuroendocrinology 2002;27:127–38.
[69] Meaney MJ, Diorio J, Francis D, Widdowson J, LaPlante P, Caldji C, et al. Early environmental regulation of forebrain glucocorticoid receptor gene expression: implications for adrenocortical responses to stress. Dev Neurosci 1996;18:49–72.
[70] Michelson D, Stratakis C, Hill L, Reynolds J, Galliven E, Chrousos G, et al. Bone mineral density in women with depression. N Engl J Med 1996;335:1176–81.
[71] Munck A, Guyre PM, Holbrook NJ. Physiological functions of glucocorticoids in stress and their relation to pharmacological actions. Endocr Rev 1984;5:25–44.
[72] Murphy BE. Antiglucocorticoid therapies in major depression: a review. Psychoneuroendocrinology 1997;22(Suppl 1):S125–32.
[73] Nemeroff CB. The corticotropin-releasing factor (CRH) hypothesis of depression: new findings and new directions. Mol Psychiatr 1996;1:336–42.
[74] Owens MJ, Nemeroff CB. Physiology and pharmacology of corticotropin-releasing factor. Pharmacol Rev 1991;43:425–73.
[75] Plotsky PM, Meaney MJ. Early, postnatal experience alters hypothalamic corticotropin-releasing factor (CRH) mRNA, median eminence CRH content and stress-induced release in adult rats. Brain Res Mol Brain Res 1993;18:195–200.
[76] Raadsheer FC, Hoogendijk WJ, Stam FC, Tilders FJ, Swaab DF. Increased numbers of corticotropin-releasing hormone expressing neurons in the hypothalamic paraventricular nucleus of depressed patients. Neuroendocrinology 1994;60:436–44.
[77] Rasmusson AM, Lipschitz DS, Wang S, Hu S, Vojvoda D, Bremner JD, et al. Increased pituitary and adrenal reactivity in premenopausal women with posttraumatic stress disorder. Biol Psychiatr 2001;50:965–77.
[78] Resnick HS, Yehuda R, Pitman RK, Foy DW. Effect of previous trauma on acute plasma cortisol level following rape. Am J Psychiatr 1995;152:1675–7.
[79] Russek LG, Schwartz GE. Feelings of parental caring predict health status in midlife: a 35-year follow-up of the Harvard Mastery of Stress Study. J Behav Med 1997;20:1–13.
[80] Sapolsky RM. Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders. Arch Gen Psychiatr 2000;57:925–35.
[81] Sapolsky RM, Pulsinelli WA. Glucocorticoids potentiate ischemic injury to neurons therapeutic implications. Science 1985;229:1397–400.
[82] Sapolsky RM, Uno H, Rebert CS, Finch CE. Hippocampal damage associated with prolonged glucocorticoid exposure in primates. J Neurosci 1990;10:2897–902.
[83] Schulkin J, Gold PW, McEwen BS. Induction of corticotropin-releasing hormone gene expression by glucocorticoids: implication for understanding the states of fear and anxiety and allostatic load. Psychoneuroendocrinology 1998;23:219–43.
[84] Schulkin J, McEwen BS, Gold PW. Allostasis, amygdala, and anticipatory angst. Neurosci Biobehav Rev 1994;18:385–96.
[85] Schweiger U, Deuschle M, Korner A, Lammers CH, Schmider J, Gotthardt U, et al. Low lumbar bone mineral density in patients with major depression. Am J Psychiatr 1994;151:1691–3.
[86] Schweiger U, Weber B, Deuschle M, Heuser I. Lumbar bone mineral density in patients with major depression: evidence of increased bone loss at follow-up. Am J Psychiatr 2000;157:118–20.
[87] Selye H. A syndrome produced by diverse nocuous agents. 1936. J Neuropsychiatr Clin Neurosci 1998;10:230–1.
[88] Sheline YI, Sanghavi M, Mintun MA, Gado MH. Depression duration but not age predicts hippocampal volume loss in medically healthy women with recurrent major depression. J Neurosci 1999;19:5034–43.
[89] Sheline YI, Wang PW, Gado MH, Csernansky JG, Vannier MW. Hippocampal atrophy in recurrent major depression. Proc Natl Acad Sci USA 1996;93:3908–13.
[90] Sloviter RS, Dean E, Neubort S. Electron microscopic analysis of adrenalectomy-induced hippocampal granule cell degeneration in the rat: apoptosis in the adult central nervous system. J Comp Neurol 1993;330:337–51.

[91] Sloviter RS, Valiquette G, Abrams GM, Ronk EC, Sollas AL, Paul LA, et al. Selective loss of hippocampal granule cells in the mature rat brain after adrenalectomy. Science 1989;243:535–8.
[92] Sorg BA, Kalivas PW. Effects of cocaine and footshock stress on extracellular dopamine levels in the ventral striatum. Brain Res 1991;559:29–36.
[93] Stein MB, Koverola C, Hanna C, Torchia MG, McClarty B. Hippocampal volume in women victimized by childhood sexual abuse. Psychol Med 1997;27:951–9.
[94] Stewart J, Badiani A. Tolerance and sensitization to the behavioral effects of drugs. Behav Pharmacol 1993;4:289–312.
[95] Swanson LW, Simmons DM. Differential steroid hormone and neural influences on peptide mRNA levels in CRH cells of the paraventricular nucleus: a hybridization histochemical study in the rat. J Comp Neurol 1989;285:413–35.
[96] Takahashi LK. Role of CRH(1) and CRH(2) receptors in fear and anxiety. Neurosci Biobehav Rev 2001;25:627–36.
[97] Takahashi LK, Ho SP, Livanov V, Graciani N, Arneric SP. Antagonism of CRH(2) receptors produces anxiolytic behavior in animal models of anxiety. Brain Res 2001;902:135–42.
[98] Takahashi LK, Turner JG, Kalin NH. Prolonged stress-induced elevation in plasma corticosterone during pregnancy in the rat: implications for prenatal stress studies. Psychoneuroendocrinology 1998;6:571–81.
[99] Trapp T, Holsboer F. Heterodimerization between mineralocorticoid and glucocorticoid receptors increases the functional diversity of corticosteroid action. Trends Pharmacol Sci 1996;17:145–9.
[100] Uno H, Lohmiller L, Thieme C, Kemnitz JW, Engle MJ, Roecker EB, et al. Brain damage induced by prenatal exposure to dexamethason in fetal rhesus macaques. I. Hippocampus. Brain Res Dev Brain Res 1990;53:157–67.
[101] Valentino RJ, Curtis AL, Page ME, Pavcovich LA, Florin-Lechner SM. Activation of the locus coeruleus brain noradrenergic system during stress: circuitry, consequences, and regulation. Adv Pharmacol 1998;42:781–4.
[102] Van Cauter E, Leproult R, Kupfer DJ. Effects of gender and age on the levels and circadian rhythmicity of plasma cortisol. J Clin Endocrinol Metab 1996;81:2468–73.
[103] Virgin Jr CE, Ha TP, Packan DR, Tombaugh GC, Yang SH, Homer HC, et al. Glucocorticoids inhibit glucose transport and glutamate uptake in hippocampal astrocytes: implications for glucocorticoid neurotoxicity. J Neurochem 1991;57:1422–8.
[104] Ward HE, Johnson EA, Salm AK, Birkle DL. Effects of prenatal stress on defensive withdrawal behavior and corticotropin releasing factor systems in rat brain. Physiol Behav 2000;70:359–66.
[105] Watanabe Y, Gould E, McEwen BS. Stress induces atrophy of apical dendrites of hippocampal CA3 pyramidal neurons. Brain Res 1992;588:341–5.
[106] Wiedenfeld SA, O'Leary A, Bandura A, Brown S, Levine S, Raska K. Impact of perceived self-efficacy in coping with stressors on components of the immune system. J Pers Soc Psychol 1990;59:1082–94.
[107] Wolkowitz OM, Reus VI. Treatment of depression with antiglucocorticoid drugs. Psychosom Med 1999;61:698–711.
[108] Yehuda R. Biology of posttraumatic stress disorder. J Clin Psychiatr 2001;62(Suppl 17):41–6.
[109] Yi SJ, Baram TZ. Corticotropin-releasing hormone mediates the response to cold stress in the neonatal rat without compensatory enhancement of the peptide's gene expression. Endocrinology 1994;135:2364–8.
[110] Yi SJ, Masters JN, Baram TZ. Effects of a specific glucocorticoid receptor antagonist on corticotropin releasing hormone gene expression in the paraventricular nucleus of the neonatal rat. Brain Res Dev Brain Res 1993;73:253–9.
[111] Young III WS, Mezey E, Siegel RE. Quantitative in situ hybridization histochemistry reveals increased levels of corticotropin releasing factor mRNA after adrenalectomy in rats. Neurosci Lett 1986;70:198–203.
[112] Zobel AW, Nickel T, Kunzel HE, Ackl N, Sonntag A, Ising M, et al. Effects of the high-affinity corticotropin-releasing hormone receptor 1 antagonist R121919 in major depression: the first 20 patients treated. J Psychiatr Res 2000;34:171–81.
[113] Zoccolillo M, Vitaro F, Tremblay RE. Problem drug and alcohol use in a community sample of adolescents. J Am Acad Child Adolesc Psychiatr 1999;38:900–7.