Chapter 10
Glucocorticoids and the Brain: Neural Mechanisms Regulating the Stress Response

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Abstract In this chapter, we describe the central role of the brain in the glucocorticoid mediated stress response. We describe the mechanisms by which the brain gauges the severity of stress, mechanisms of hypothalamic-pituitary-adrenal axis (HPA) regulation, and how various sub-systems of the brain respond to glucocorticoid (GC) signaling to regulate stress behavior. In particular, we focus on the hippocampus, pre-frontal cortex, and amygdala, where GCs can induce a series of changes. Finally, we briefly discuss an apparent paradox in GC signaling: while exposure to glucocorticoids promotes the survival of an organism during acute stress, these same hormones in chronic excess can also cause damage and promote illness.

Keywords Stress • HPA axis • Negative feedback • Glucocorticoids • Behavior • Amygdala • Prefrontal cortex • Hippocampus

Introduction

Organisms face a wide variety of environmental conditions that can perturb homeostasis. To effectively respond to these "stressors," the organism must initiate a coordinated response across a variety of physiological systems. For example, the

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organism must perceive the stressor and select appropriate behavioral strategies (brain) and optimize energy resources towards a "fight, flight or freeze" response (cardiac, respiratory, skeletal) in part by shutting down systems that are not immediately essential (digestive, reproductive, growth).[1] In the vertebrate stress response, the activation of these various systems is initiated by the release of glucocorticoid (GC) stress hormones from the adrenal glands, and also by catecholamine signaling. Importantly, the stressful situations that an organism encounters are diverse. Stressors may be acute and severe (e.g., predation), chronic and severe (e.g., drought), or mild (e.g., social interactions) and each type of stressor requires a unique adaptive response. On the other hand, some types of challenges are predictable, and in these cases GC secretion can allow the organism to prime its physiological response in anticipation of the pending challenge. For example, in diurnal animals GCs are secreted in a daily circadian cycle, with high GC secretion inducing arousal during the early morning and a GC trough promoting rest during the evening. To respond to these wide variety of environmental challenges, ranging from mild to severe and predictable to unpredictable, vertebrates have evolved a complex regulatory system, the hypothalamic-pituitary-adrenal (HPA) axis, to perceive the severity of environmental challenge and release an appropriate amount of GCs for a measured, homeostatic behavioral response.

In this chapter, we describe the central role of the brain in the GC-mediated stress response. We describe the mechanisms by which the brain gauges the severity of stress and initiates an appropriate systemic response—in other words, regulation via the HPA axis. Secondly, we describe how various sub-systems of the brain respond to GC signaling to regulate stress behavior. In particular, we focus on the hippocampus, pre-frontal cortex, and amygdala, where GCs can induce a series of changes (Fig. 10.1). These include alterations that underpin behavioral responses such as alertness and cognitive function, appetitive versus aversive thresholds to various threatening stimuli and rewards (i.e., motivation vs. avoidance), fear, and memory formation. On a cellular and molecular level, this entails modulations of neurotransmitter levels, alterations in dendritic morphology, receptor density, and changes in signal transduction. Thirdly, we briefly discuss an apparent paradox in GC signaling: while exposure to glucocorticoids promotes the survival of an organism during acute stress, these same hormones in chronic excess can also cause damage and promote illness. Chronic stress is a risk factor for multiple diseases, including diseases of central and peripheral nervous systems such as stroke, mental illness, and multiple sclerosis [122–127]. Within the CNS, chronic glucocorticoid exposure can suppress neurogenesis, bias cell fates of neural precursor cells, contribute to dendritic atrophy, and alter neuronal excitability in key regions of the brain involved in anxiety and depression [reference]. Therefore, an organism's best option is to mount as efficient a stress response as possible, limiting its exposure to high levels of catabolic and metabolically demanding glucocorticoids. Fine-tuning of the stress

[1] Hans Selye, the father of modern stress research defined stress as the "non-specific response of the body to any demand made upon it" [96].

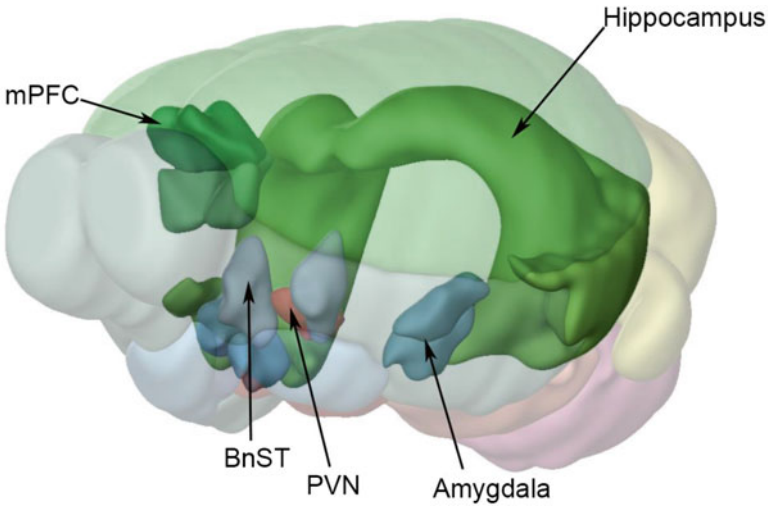

Fig. 10.1 Selected limbic structures involved with HPA axis regulation

response can have a dramatic influence on health. Importantly, the calibration and reactivity of the stress response is partly dependent upon early life environmental contexts and developmental programming, which help prepare organisms for future and current environmental challenges.

The Hypothalamic-Pituitary Adrenal Axis

As a first step in activating the HPA axis, the brain integrates external and internal sensory information pertaining to the immediate challenge, and this information is transduced into endocrine responses within the paraventricular nucleus of the hypothalamus (PVN) [45]. The hypophysiotropic neurons within the PVN secrete corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) into the hypophyseal portal system, a system of blood vessels that link the hypothalamus with the pituitary gland. Upon reaching the anterior pituitary, CRH stimulates the release of adrenocorticotropic hormone (ACTH) into circulation. Elevated ACTH levels, in turn, stimulate the synthesis and release of glucocorticoids via binding to melancortin-2 receptors within the cortex of the adrenal glands [1]. HPA activation results in a maximal rise in circulating GCs after 15–30 min, and returns to baseline levels at roughly one hour after the termination of a stressor [93]. The crucial ability to terminate the stress response, or inhibit the secretion of CRH and ACTH, is via glucocorticoid negative feedback on key neural regions, such as the PVN, anterior pituitary, medial prefrontal cortex (mPFC), and hippocampus.

The stress response, as a whole, does not solely depend on GCs to alter physiology and behavior—it also requires the concerted actions of several other neuropeptides. These include: urocortins, which interact with CRH; vasopressin, which is implicated in stress-related social memory and emotionality; and orexins, which are involved with stress-related energy and circadian homeostasis. Furthermore, CRH acts in many other brain regions outside of the PVN of the hypothalamus. For example, CRH is released in the bed nucleus of the stria terminalis (BnST) where it plays a role in stress-related anxiety. In the nucleus accumbens, CRH acts to suppress dopamine release in response to rewards, and shift appetitive and aversive behaviors [61, 113] while in the amygdala and in the hippocampus it is involved in stress-related emotional memories, anxiety, and learning processes [89, 92]. A review of the actions of GCs on the brain is incomplete without considering the coordinated influence of the aforementioned peptide mediators, however, its discussion exists outside the scope of this chapter. For an excellent review of CRH, see [53].

HPA Negative Feedback

The ability of the HPA axis to respond dynamically to stress or to tonic secretion of glucocorticoids via circadian rhythm is determined, in part, by the ability of glucocorticoids to adjust ACTH secretion. This negative feedback occurs when GCs penetrate the blood–brain barrier and exert rapid (non-genomic) and slower (genomic) effects on the various neural regions that regulate ACTH release [24, 38, 101]. Two classes of brain steroid receptors mediate negative feedback: the mineralocorticoid receptor (MR), and glucocorticoid receptor (GR). Both MR and GR belong to the nuclear receptor superfamily and function as transcription factors regulating gene expression [85].

MRs have a relatively limited distribution, exhibiting the highest expression within the subiculum/CA1 field and dentate gyrus of the hippocampus [85] (Fig. 10.2a). GRs are expressed nearly ubiquitously (Fig. 10.2b). There are, however, areas of greater GR density within the hippocampus, amygdala, cerebellum, hypothalamus (most notably the PVN), neurons of the ascending aminergic pathways of the brainstem, and to a lesser extent, the caudate nucleus and putamen [34, 78]. While both receptor subtypes bind corticosterone, MRs have a roughly tenfold greater affinity for GCs relative to GRs (Kd of ~0.5 nM for MR vs. Kd ~2.0–5.0 nM for GR) [85]. Consequently, MRs preferentially bind GCs over GRs and reach near-saturation levels during troughs of the circadian cycle (i.e., low basal levels), and are fully saturated during circadian peaks and stress. GRs are activated only when glucocorticoid levels reach a high concentration beyond the level that saturates MRs, such as during an acute stressor or during the zenith of the circadian rhythm. It is hypothesized that MRs are a critical component of the circadian regulation of baseline HPA tone (via fast-feedback, non-genomic actions), while GRs, occupied at higher corticosteroid concentrations, mediate feedback actions following stress [7]. Thus, the balance of MR and GR receptor types, their occupancy, and

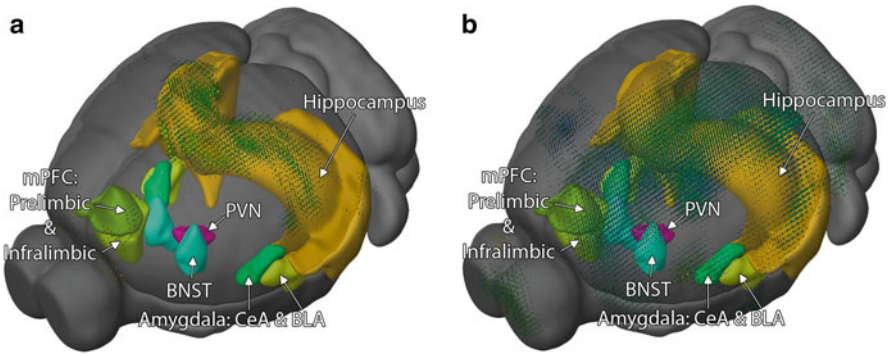

Fig. 10.2 (**a**) MR distribution in the mouse brain. (**b**) GR distribution in the mouse brain

their associated mechanism of action are intricately involved in HPA regulation. Might be worth citing the papers where they make tissue specific KO of GR in hypothalamus or hypothalamus + GR and get Cushings syndrome.

Major Brain Structures Involved in HPA Regulation

Four brain regions are strongly implicated as sites for HPA regulation and synthesis of CRH and AVP. These include the PVN of the hypothalamus, frontal cortex, amygdala and hippocampus.

Paraventricular Nucleus of the Hypothalamus

The PVN is the main gateway for initiating the hormonal stress response, and thus a primary target for regulating HPA negative feedback. It contains one of the densest populations of CRH neurons, which express GRs [17, 110]. Exogenous application of GCs in the PVN results in a rapid decrease in CRH mRNA expression [56] leading to a corollary decrease in HPA activation. Conversely, lesioning PVN afferents serves to increase expression of CRH and AVP mRNA demonstrating that neuronal inhibitory pathways are also necessary for the maintenance of HPA tone [44, 45].

Non-genomic, fast feedback inhibition of the HPA axis within the PVN is dependent on both endocannabinoid and GABAergic mechanisms [106]. GCs stimulate the synthesis and release of endocannabinoids within the PVN by binding to membrane-bound MRs. These endocannabinoids then bind to presynaptic CB1 receptors to suppress glutamatergic transmission, thus inhibiting the activation of PVN neurons and reducing secretion of CRH [24, 29, 48]. GCs also bind to receptors on inhibitory magnocellular neurons of the PVN to stimulate fast, G-protein-dependent

release of GABA to inhibit downstream CRH secretion [106]. In this fashion, MRs act in a rapid, non-genomic pathway for negative feedback within the PVN of the hypothalamus.

Medial Prefrontal Cortex

In rodents, the medial prefrontal cortex (mPFC) is comprised of infra-limbic (IL), pre-limbic (PL), and anterior cingulate cortices (AC) (based on structural connectivity and function, these areas are thought to be homologous to human Brodman areas 25, 32 and 24b respectively) [111, 112]. The mPFC is a region of the brain that is involved in cognitive and executive functioning, including working memory, the ability to shift attention across perceptual dimensions, and rule-guided action to plan and guide behavioral sequences. Receiving diverse afferent inputs from the amygdala and ventral hippocampus, as well as providing direct efferent connections to hypothalamic and monoamine brain nuclei, the mPFC is well situated to regulate cognitive, emotional and physiological responses to stress [13].

The mPFC is highly involved in autonomic control and HPA inhibition [2, 6, 75]. Evidence for HPA suppression arises from lesion studies in which mPFC lesions lead to significantly increased plasma levels of ACTH and corticosterone following restraint stress and increased c-Fos activation in the PVN and medial amygdala [10, 27, 31, 102]. Furthermore, local injections of corticosterone into the mPFC are capable of dampening plasma levels of these same hormones [3]. However, exposure to chronic stressors, such as 4 weeks of daily restraint, leads to a down regulation of GR mRNA and protein levels in the PFC, resulting in attenuated PFC-mediated HPA negative feedback [74]. Of note, the primate brain expresses significantly different GR and MR distributions compared to rodents. In primates, GR levels are in greater abundance in the mPFC than the hippocampus, where there is a relative paucity in expression [91]. This suggests that the primate PFC may play a larger role in GR mediated feedback than the hippocampus.

The mPFC influence over the HPA axis is both intra-region specific and exhibits hemispheric functional lateralization [84, 102]. Pre-limbic and infra-limbic cortices exert opposing control over HPA tone. The pre-limbic cortex can be thought of as the ‘brakes’ whereas the infra-limbic cortex can be considered the ‘gas pedal’ of HPA regulation. Electrical stimulation of pre-limbic cortex activates parasympathetic systems, whereas infra-limbic stimulation results in robust HPA activation. More recent work has confirmed that this dual control of HPA regulation is GR dependent. GR knockdown in pre-limbic or infra-limbic cortices via short-hairpin RNA leads to differential regulation of HPA secretion, such that infra-limbic disruption leads to HPA hyper-reactivity, while pre-limbic GR knockdown contributes to stress hypo-reactivity in response to an acute psychogenic stressor [70].

HPA control also exhibits hemispheric lateralization. HPA activation is markedly lower after right mPFC lesions, but not left [102]. HPA axis down-regulation after

right mPFC lesion was found to be greater in response to chronic stress than to acute stress, suggesting that the mPFC is associated with regulating HPA activity during highly stressful conditions [13].

Intra-region specificity of the mPFC (brake vs. gas) is stressor specific. It modulates its responses based on the nature of the environmental challenges presented, such as psychological stress vs. physical stress. The pre-limbic cortex (brake) is of particular note in its role in inhibiting the HPA axis, especially with respect to psychogenic stressors. This is evidenced by inhibition of CRH and AVP expression after GC infusion into mPFC during restraint stress, a psychological stressor, but not the anesthetic ether, a physical stressor. Conversely, the infra-limbic cortex can initiate HPA activity. It responds robustly to both physical and psychogenic stress [70, 84, 103]. For instance, repeated social stress, but not noise stress, significantly increases ΔFosB expression, an immediate early gene used as a marker for neuronal activation, within the infra-limbic mPFC [50]. This suggests that the mPFC plays a role in the ability to discriminate between psychogenic and physical stressors, thereby increasing the efficiency and specificity of HPA axis regulation [27, 31, 84].

Similarly to the PVN, mPFC-mediated HPA inhibition is dependent in part on GR-mediated endocannabinoid signaling. CB1 receptor antagonism within the mPFC up-regulates HPA activity and results in prolonged GC secretions. Furthermore, GC exposure results in endocannabinoid release, indicating homeostatic negative feedback. Mechanistically, increases in endocannabinoids lead to a decrease in GABA release. This results in a net gain in excitation on pre-limbic (brake) neurons [49]. The pre-limbic cortex has direct afferents onto GABAergic neurons within the BnST, which in turn send projections to the neurosecretory cells of the PVN. In this fashion, GC-induced CB1 activation of the pre-limbic mPFC results in an activation of inhibitory BnST-PVN circuitry. The net result is the suppression of HPA activity.

Responding to psychogenic and physiological stressors, the mPFC is a key component in the top-down regulation of the HPA axis. Part of this regulation is mediated by serotonergic mPFC-amygdala connectivity [32]. For example, decoupling serotonergic mPFC-amygdala circuitry leads to alterations in stress related behaviors [5, 116]. However, the amygdala also regulates the mPFC, thus is another critical component in the emotional guidance of behavior [26].

Amygdala

Receiving direct and indirect connections from limbic structures, including mPFC and hippocampus, the amygdala is thought to be a major integrating center for emotional and arousing stimuli. The amygdala is highly involved in the systemic stress response and is sensitive to both glucocorticoids and catecholamines. Direct stereotactic infusions of GC to the amygdala greatly increase CRH mRNA expression within the PVN during psychogenic stress, illustrating the amygdala's capacity to alter HPA activity during elevated GC exposure [97].

Like the mPFC, the amygdala's influence over HPA systems is region specific. The amygdala is a complex of many sub-nuclei, often segregated into three regions: corticomedial (MeA), central (CeA), and basolateral (BLA) nuclei groups [100]. The CeA is further divided into a lateral component (CeL), and a medial (CeM) component. The balance of excitation and inhibition in each of these sub-regions modulates HPA reactivity [12, 68, 98, 100]. The amygdala has both "anxiogenic" and "anxiolytic" pathways. Stimulation of the BLA itself has been shown to increase HPA activity (anxiogenic), while direct stimulation of the CeM, results in anxiolytic effects. Since both the CeA and the BLA sends projections to the PVN via the BNST, the net effect of amygdala activation on the HPA axis is contingent upon the circuitry that is invoked [80, 109].

Hippocampus

Involved in cognition and memory formation, the hippocampus is a critical locus in HPA regulation. It exhibits tremendous plasticity to stress and glucocorticoids. Within the rodent brain, the hippocampus expresses the highest level of GR and MR, hence, it is of little surprise that it serves as an important negative feedback center and regulator of the stress response [46]. Evidence for HPA negative feedback arises from early studies in which lesioning or blocking hippocampal GC receptors results in an up-regulation of CRH and AVP mRNA within the PVN. The consequence of this is hypersecretion of glucocorticoids [52, 93]. Conversely, activation of hippocampal GC receptors results in HPA axis inhibition [93].

However, the relationship between hippocampus and HPA regulation are specific to particular hippocampal sub-regions. Structurally and functionally heterogeneous, the hippocampus can be segregated across a septotemporal axis [8, 30]. In rodents, the dorsal hippocampus appears to be more involved in learning and memory, while the ventral hippocampus is implicated in the modulation of anxiety-like behavior and HPA regulation [8]. Lesions to dorsal hippocampus result in spatial memory deficits, whereas ventral hippocampal lesions result in anxiety-like behaviors alterations [8, 30, 79]. These differences in function can be explained in part by the connectivity of each region. For instance, regions of the ventral hippocampus project to areas involved in emotional regulation, most notably, the mPFC, amygdala, BnST, and the PVN [30].

The hippocampus is also one of two brain regions in which resident populations of neural stem cells (NSCs) produce new neurons in adult animals [33, 35]. These new neurons are thought to contribute to the plasticity of hippocampal networks and have roles in the classical hippocampal functions of learning and memory. However, several lines of recent evidence also suggest that NSCs play a role in HPA regulation. First, chronic, but not acute, activation of hippocampal GRs is associated with a general *increase* in HPA reactivity [86]. This failure in HPA axis negative feedback may be due, in part, to a reduction of the neurogenic pool resulting from chronic GC exposure. More direct evidence comes from ablation of hippocampal

neurogenesis, through the use of techniques such as irradiation or by transgenic animal models, which results in impaired HPA negative feedback and elevated GC levels following recovery from restraint stress [99]. Animals with impaired neurogenesis also exhibit a depressed phenotype at baseline that can be reversed by antidepressant treatment [99]. Lastly, hippocampal neurogenesis appears to be required for antidepressants to restore HPA axis inhibition following chronic stress [104]. Taken as a whole, these and other findings have implicated hippocampal neurogenesis as a component of HPA axis regulation.

Effects of GCs on Brain and Behavior

As described above, many brain regions that integrate sensory information, such as the mPFC, amygdala, and hippocampus, can exert control of the PVN to fine tune the stress response according to the immediate experiences of the animal. In turn, once the stress response is initiated, the animal also has to enact appropriate behavioral strategies to cope with the stressor. Thus, beyond acting as a negative feedback signal, GCs also modulate brain function in these same regions to coordinate appropriate stress-response behaviors.

Medial Prefrontal Cortex

Stress, both mild and severe, can lead to functional and structural changes in the prefrontal cortex [6, 39, 51]. This includes alterations in dendritic arborization and spine density in all regions of the mPFC (IL, PL, and AC) and neighboring orbitofrontal cortex, which is driven in part, by GR signaling [11, 15, 62, 63, 82, 121]. For instance, 3 weeks of corticosterone administration [115] or daily restraint stress [20], is capable of reducing dendritic arborization and spine density in the mPFC and dorsomedial striatum [21, 25]. Functionally, both glucocorticoid administration and stress leads to deficits in working memory [11, 15, 76, 90], mPFC dependent set-shifting [63], as well as reversal learning [14, 15, 60].

Paradoxically, under some conditions, chronic stress can facilitate reversal learning [40, 41]. One hypothesis by Dias-Ferreira and colleagues as well as Schwab and Wolf, posits that stress leads to a disinhibition of PFC functions and towards striatal mediated learning [25]. The effect is bias in an organism's behavior towards habit formation [25, 41, 94, 95]. Indeed, severe, repeated stressors result in an increase in apical dendrite arborization in both the dorsolateral striatum and orbitofrontal cortex, regions involved in habitual strategies, reward valuation, and reversal learning [25, 63]. These studies suggest that the effects of stress and glucocorticoids may be beneficial to shift behaviors toward optimal behavioral adaption to environmental stress.

Amygdala

Its activation by GCs can lead to alterations in learning and memory [88]. However, it is important to note that amygdala contributions to autonomic functioning are with respect to emotional arousal, not circadian or homeostatic HPA regulation.

Both acute and chronic stress results in the remodeling of synapses and dendritic branching within the amygdala [72, 73]. Stress induced synaptic plasticity is modulated by GABAergic inputs [23]. These changes are correlated with an increase in anxiety-like behaviors and enhanced fear conditioning [19, 73, 118]. High levels of corticosterone reduce GABA transmission, which results in an increase in the firing rate of excitatory neurons in the basolateral amygdala [28]. This suggests that high levels of glucocorticoids can change the balance between excitation and inhibition, resulting in modifications in synaptic connectivity. These changes can influence neuronal plasticity even in distal brain regions. Recent findings demonstrate that the BLA can alter synaptic plasticity and long-term potentiation in the striatum and hippocampus. Therefore, it is becoming increasingly clear that glucocorticoids within the amygdala can be far-reaching and impactful [4, 81].

Finally, the amygdala also plays a central role in enhancing memory consolidation following emotionally arousing events. High levels of circulating GCs can improve the recall of a stressful event [9, 77, 89]. However, GCs effects may be mediated by ß-adrenergic activation; blockade of ß-ardrenergic receptors within the BLA prevents memory enhancements following GR activation. Furthermore, activation of BLA via emotional arousal is critical in GC-mediated memory enhancements [83]. Enhanced memory performance following a stressful event can be advantageous, as future encounters to similarly arousing stimuli would result in a feed-forward HPA activation to prime physiological systems in anticipation of a stressor. However, more investigations are needed to fully determine how stress, NE, and GCs influence different phases of fear learning and its expression in memory.

Hippocampus

The hippocampus responds dynamically to changes in GCs levels by modulating neuronal structure and function. GCs directly influence hippocampal function by acting as neuromodulators to influence neural excitability and signaling [16, 54, 55, 59, 64]. More broadly, GCs also affect the structural connectivity of the hippocampus by affecting dendritic arborization and formation of synapses [114, 119, 120]. Together, a model has emerged from these studies in which mild or acute stress increases hippocampal dendritic branching and long-term potentiation to boost hippocampal learning and memory, while chronic or high GC concentrations have opposite effects [19, 47, 58, 92]. However, the distribution of MR and GR receptors differs in dorsal versus ventral hippocampus, with ventral hippocampus having a

much higher relative concentration of MR [87]. This suggests that the effect of stress on hippocampal function may be more nuanced and region-specific, such that high levels of GCs do not simply suppress hippocampal memory function in general, but rather specifically suppress the contextual memory functions of dorsal hippocampus while promoting the emotional cognitive functions of the ventral hippocampus [65, 66]. This model fits well with the overall paradigm of the stress response as an adaptive mechanism that manifests stress-specific behavioral strategies suited to overcoming stressful challenges [65, 66].

Stress effects on hippocampal-mediated behaviors may also be regulated through the contributions of hippocampal NSCs. NSCs express functional GRs (but not MRs) [18, 36], and their rate of proliferation and differentiation, as well as the survival of the new neurons that they produce, are altered by GCs [58, 117, 128–130]. The effects can be via direct activation of GR in the NSC [36] or indirectly, through activation of GR-dependent mechanisms in other cells in the hippocampal niche. For instance, acute corticosterone exposure elicits release of fibroblast growth factor-2 from astrocytes in the dorsal hippocampus, leading to increased proliferation of neural stem cells in the area [58].

The effects of stress on adult neurogenesis can be divided into the effects of acute stress and repeated, chronic stress. Chronic, repeated stressors inhibit NSC survival, proliferation, and neuronal differentiation within the dentate gyrus [57, 71, 117]. However, the effects of acute stress display a more mixed picture, ranging from a decrease, increase, or no change in NSC proliferation [22, 43, 107, 108]. One explanation for discrepancies in the literature may be that, like cognitive performance in response to stress, adult hippocampal neurogenesis follows an inverted U function—increasing in response to acute stressors and decreasing in response to high, chronic GC exposure. For example, high levels of transient GCs can inhibit NSC proliferation in the SGZ, and this effect can be blocked through adrenalectomy [105].

Beyond proliferation, high levels of GCs may also reduce the total number of new neurons by decreasing the survival of immature neurons as they begin to incorporate into the network [117]. Furthermore, GCs cause a shift in the cell fate of differentiation NSCs, causing them to more frequently differentiate into oligodendrocytes at the expense of neurogenesis [18]. Given that new neurons ultimately confer additional plasticity onto hippocampal networks, by forming new synaptic connections and showing enhanced capacity for LTP [37, 42, 67], the reductions in neurogenesis in response to elevated GCs may be one of the mechanisms underlying reduced memory capacity in stressed animals.

Conclusion

Glucocorticoids regulate the brain and behavior in multiple domains. They help adjust basal and peak HPA axis reactivity [93], as well as alter limbic structures (PVN, mPFC, amygdala, hippocampus), both structurally and functionally. This includes alterations in synaptic plasticity, long-term potentiation, and neurogenesis,

which result in changes in appetitive and avoidant behaviors, and modifications in learning and memory. Additionally, the limbic system is responsible for the top-down and bottom-up regulation of the HPA axis through its complex micro-circuitry. In this sense, HPA regulation can be a recursive process since glucocorticoids modulate both initiators and terminators of the stress response.

Ultimately, stress is necessary for the optimization of behavior to environmental pressures. With respect to humans, it is HPA axis dysregulation that is implicated in the pathogenesis of many disease phenotypes such as anxiety and depression [69]. It is of paramount importance to efficiently initiate a stress response, as it promotes survival, while equally important to terminate the stress response, as glucocorticoids are metabolically demanding and can lead to disease.

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