Abstract

Stress leads to increased activity of the sympathetic nervous system (SNS) and of the hypothalamic-pituitary-adrenal (HPA) axis. Stimulation of the latter induces the release of glucocorticoids (GCs) from the adrenal cortex. The multiple effects of GCs in the brain are the focus of the current chapter. Acute stress effects comprise the enhancement of long-term memory consolidation and the simultaneous impairment of memory retrieval. Moreover, a qualitative shift away from a cognitive response style toward a more stimulus-driven habitual response style occurs. The acute response to GCs is altered in major depressive disorder and posttraumatic stress disorder. Chronic stress causes structural alterations in the hippocampus and the medial prefrontal cortex in the form of dendritic atrophy. However, remaining plasticity and thus the potential to reverse these changes appears to be more common than previously thought. The advanced understanding of the central nervous system effects of GCs will ultimately lead to progress in the treatment of mental and systemic diseases characterized by HPA axis dysregulation.

INTRODUCTION

Stress has a bad reputation in present-day societies. It is typically associated with physical and mental health problems. However, research over the past decades has illustrated that the impact of stress on brain functions such as learning and memory are far more complex than initially assumed. Stress may enhance or impair memory depending on several key modulators and mediators. Both quantitative and qualitative shifts take place.

Everyone has experienced episodes in which stress influenced their memory. There are situations in which we are unable to retrieve previously well-learned information, an example of how stress might interfere with our memory. In contrast, we tend to remember specific embarrassing, shameful, or frightening events from the past very well. This is an example of how stress can
enhance our memory. Finally, there are conditions such as chronic stress or stress-associated mental disorders which are characterized by specific memory dysfunctions. The goal of the present chapter is to provide a brief and focused overview of current knowledge on the role of glucocorticoids (GCs) in mediating these stress effects. Advances in the field of psychoneuroendocrinology within the past decades have contributed to a more differentiated and balanced view of the effects of stress hormones on memory in animals and humans.

**KEY POINTS**

- Acute stress enhances long-term memory consolidation but impairs its retrieval
- Stress causes a shift to a more habitual—stimulus-driven—response style
- The impact of glucocorticoids on memory is altered in mental disorders
- Early life stress programs a vulnerable phenotype via epigenetic mechanisms
- Chronic stress induces dendritic atrophy in the hippocampus and the medial PFC
- In contrast, chronic stress leads to hypertrophy in the amygdala and the striatum
- Reinstating appropriate HPA signaling appears to be a promising therapeutic target in mental disorders associated with altered HPA axis activity.

**DEFINITION OF STRESS**

A common definition is that stress occurs when a person perceives a challenge to their internal or external balance (homeostasis). Thus, a discrepancy between what “should be” and “what is” induces stress. A stressor can be physical (e.g., heat, thirst) or psychological (e.g., work overload, unemployment, mobbing, marital problems), as well as acute or chronic. The subjective evaluation of the stressor and of available coping resources determines its impact on the individual. Something perceived as a threat by one person might be perceived as an exciting opportunity by another. There is substantial interindividual variability in the response to stress. For humans as social animals, a threat to the social self (social evaluative threat), in combination with uncontrollability of the situation, is especially potent in triggering a stress response.

**THE TWO STRESS SYSTEMS: HPA AND SNS**

Stress leads to neuroendocrine responses aimed at facilitating adaptation. In this context, the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS) play important roles. SNS activity leads to the rapid release of (nor) epinephrine from the adrenal medulla. This constitutes the first rapid response wave. Increased activity of the HPA axis leads to the release of GCs (cortisol in humans, corticosterone in most laboratory rodents) from the adrenal cortex. This response is slower and constitutes the second response wave. GCs are lipophilic hormones that can enter the brain, where they influence regions involved in cognitive functions (e.g., amygdala, hippocampus, prefrontal cortex (PFC), striatum). These effects are mediated by the two receptors for the hormone: the mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR). They differ in their affinity for GCs and in their localization. While MR activation leads to enhanced neuronal excitability, GR activation causes a delayed suppression or normalization of the neuronal network. In addition, GCs can exert rapid nongenomic effects which, in part, are mediated by recently described membrane-bound MRs and GRs. Thus GCs have time-dependent effects comprising of early rapid nongenomic effects and later occurring slower genomic effects.

After acute stress, the HPA axis’ negative feedback system leads to GC levels returning to baseline values within hours. In periods of chronic stress, persistent alterations of the HPA axis can occur, leading to continuously elevated cortisol concentrations. However, elevated cortisol levels as typically observed in major depressive disorder (MDD) are not always the consequence of chronic stress. For example, reduced cortisol levels occur in several stress-associated somatoform disorders as well as in posttraumatic stress disorder (PTSD).

**STRESS AND COGNITION: ACUTE EFFECTS**

Stress affects the central processing of incoming information at multiple levels. Early influences on perception, attention, and working memory have been documented, as well as later effects on long-term memory. Initially, stress causes an increase in vigilance which goes along with a reduction in top-down cognitive control processes. Working memory and executive functions are typically impaired during and shortly after stress exposure. The present chapter will focus on the influence of stress on learning and memory. This topic has received a lot of attention during the past years, and our knowledge concerning it has consequently improved substantially. Long-term memory can be subdivided into declarative or explicit and nondeclarative or procedural (implicit) memory. Based on its content, declarative memory can be further subdivided into episodic memory (recall of a
specific event which can be located in space and time) and semantic memory (our knowledge of the world). The medial temporal lobe is critical for declarative memory, with the hippocampus being especially important for episodic memory.\(^1^\)

Long-term memory can also be subdivided into different memory phases, namely acquisition (or initial encoding), consolidation (or storage), and retrieval (or recall). During the 1990s, the literature regarding the effects of stress on episodic memory in humans was somewhat confusing, with groups reporting both enhancing as well as impairing effects of GCs on long-term memory. However, it has become evident that this is largely due to the fact that the different memory phases outlined above are modulated by GCs in an opposing fashion.\(^2^,\(^3^\)

GCs enhance memory consolidation; this process representing the adaptive and beneficial side of the action of GCs in the central nervous system (see Fig. 31.1). It has been conceptualized as the beneficial effects of “stress within the learning context” or “intrinsic stress.” This wording emphasizes the fact that a stressful episode is remembered better than a nonstressful one, an effect which is mediated by the action of stress-induced GCs. Lesions of the hippocampal formation and which has been very well documented in rodents. Studies have shown that an adrenergic activation in the basolateral amygdala (BLA) is a prerequisite for the modulating effects of GCs on other brain regions (e.g., the hippocampus). Lesions in the BLA as well as beta blockade abolish the enhancing effects of postencoding GC treatment.\(^2^,\(^7^\)

Comparable effects have been observed in humans: immediate postacquisition stress has repeatedly been linked to boosted memory consolidation. Converging evidence comes from pharmacological experiments. Cortisol administration shortly before memory encoding caused enhanced long-term memories especially for emotional learning material. Moreover, neuroimaging studies have characterized a stress-induced modulation of the amygdala and hippocampal activity as the neural correlate of these effects.\(^3^,\(^5^\)

Preencoding stress or cortisol studies have led to a less consistent picture. Reports of enhancing as well as impairing effects can be found. In this case, the exact timing of the stressor, the emotionality of the learning material,\(^2^,\(^4^\) the relation of the learning material to the stressor, and the delay between encoding and retrieval\(^3^\) appear to be important modulatory factors.\(^3^,\(^5^\)

While an enhanced memory consolidation is adaptive and beneficial, this process appears to occur at the cost of impaired memory retrieval (see Fig. 31.1). Using a 24-h delay interval, researchers were able to show that stress or GC treatment shortly before retrieval testing impairs memory retrieval in rats in a water maze.\(^5^\) Further studies have revealed that, once again, an intact BLA as well as its adrenergic activation appear to be necessary for the occurrence of this negative GC effect.\(^2^,\(^7^\) Roozendaal has summarized these findings as indicative of stress putting the brain into a consolidation mode accompanied by impaired retrieval. Such a reduction in retrieval might facilitate consolidation by reducing interference. In humans, multiple studies have been able to demonstrate a stress-induced retrieval impairment using different stressors and different memory paradigms. Similar impairments occur after pharmacological administrations of GCs.\(^3^,\(^5^\) These behavioral effects are accompanied by reduced neural activity in the hippocampus, as demonstrated using functional magnetic resonance imaging.\(^2^,\(^3^\)

Of note, the beneficial effects on consolidation as well as the impairing effects on retrieval are more pronounced for emotionally arousing learning material. This observation fits the mentioned observation in rodents that GCs can only exert effects on memory in the presence of adrenergic activity in the amygdala. This arousal can apparently result from specifics of the learning material and/or specifics of the testing conditions.\(^1^,\(^5^\)\(^,\(^7^\)\) In sum, studies in animals and humans converge on the idea that GCs acutely enhance long-term memory consolidation while impairing memory retrieval (see Fig. 31.1).

More recently, evidence has accumulated that stress may also influence extinction retrieval in classical (fear) conditioning paradigms.\(^1^\) The fear memory trace initially created during acquisition is not erased during extinction. Rather, extinction leads to a second inhibitory memory trace which is dependent on prefrontal brain regions. This inhibitory trace is considered to be context dependent and state dependent, as illustrated by several recovery phenomena (e.g., renewal, reinstatement, spontaneous recovery; see Ref. \(^2^,\(^5^\)\) Stress, via its impact on the amygdala and PFC, might impairextinction retrieval,\(^1^\) thus leading to the return of fear.\(^1^\) This hypothesis needs further evaluation but has substantial clinical relevance as it could explain the clinical observation that stress in patients is often associated with the reoccurrence of symptoms.

---

**FIGURE 31.1** Phase-dependent effects of stress on long-term memory. Immediate postacquisition stress enhances memory consolidation, as indicated by the green arrow and the plus sign. This causes enhanced memory retrieval hours, days, or weeks later. In contrast, stress shortly before memory retrieval impairs long-term memory by temporarily blocking the accessibility of the memory trace. This is indicated by the red arrow and the minus sign. Preencoding stress has variable effects on long-term memory (thus yellow and +/- which are mediated by the exact timing of the stressor, the emotionality of the learning material and the delay between encoding and retrieval.

---

II. ENDOCRINE SYSTEMS AND MECHANISMS IN STRESS CONTROL
Cortisol as an Adjuvant Treatment for Psychotherapy?

De Quervain and colleagues have tested the hypothesis that the impairing impact of cortisol on emotional memory retrieval in combination with the enhancing effects of cortisol on memory consolidation might be beneficial in the context of the psychotherapeutic treatment of anxiety disorders. When patients are confronted with the fear-inducing stimulus during therapy (e.g., with a spider or with heights), cortisol may block the retrieval of previous fearful memories. Moreover, cortisol could enhance the storage of the new extinction memory trace.7 Support for this model comes from several studies with different patient populations. Repeatedly, they were able to demonstrate that cortisol administration before exposure therapy sessions enhanced the effectiveness of the intervention compared to a placebo control condition.6 These findings open up a new avenue of research aimed at supporting or boosting the success of psychotherapeutic treatments by using endogenous hormones.

Altered Acute Effects of GCs in Mental Disorders?

Several mental disorders, including MDD, PTSD, and borderline personality disorder (BPD), are characterized by dysregulation of the HPA axis and memory dysfunction. These pathological hallmarks appear to be associated with each other. However, as of today, only a few studies have investigated the acute effects of cortisol (or stress) in these disorders.

Patients with MDD often show HPA axis hyperactivity with elevated corticotropin-releasing hormone (CRH) levels, elevated cortisol levels, and impaired negative HPA axis feedback. An enhanced central CRH drive and/or impaired GR functioning might contribute to these neuroendocrine abnormalities.32 In a series of studies, Wingenfeld and colleagues could reveal that MDD patients, in contrast to healthy controls, do not exhibit an impairing effect of cortisol on memory retrieval (see Fig. 31.2). This might be behavioral evidence for a reduced functioning of central GRs.33

Patients with PTSD, on the other hand, are characterized by different HPA-related findings. Here, enhanced negative feedback and reduced basal cortisol levels are typically found,40 even though the empirical picture is somewhat heterogeneous. This might, in part, be due to different comorbidities and different vulnerability patterns. Strikingly, PTSD patients showed an enhanced rather than impaired memory retrieval after cortisol administration in several studies35 (see Fig. 31.2). Similar findings have been obtained in patients with BPD. The interpretation of these findings is more challenging. One might suggest that the beneficial effects of acute cortisol elevations on memory processes mediated by the hippocampus could be due to enhanced GR functioning. However, findings on GR sensitivity in PTSD are inconclusive, and comparable studies on BPD patients are missing completely. Furthermore, the role of the MR as well as the MR/GR balance in this context is not well understood. Alternatively, memory improvement after cortisol administration could be interpreted in the context of inhibition of central corticotropin-releasing factor (CRF) release through cortisol administration.33

The question arises as to how this research is to transfer into treatment strategies. In PTSD patients, for example, there is initial evidence that GC administration might reduce the involuntary retrieval of aversive memories (flashbacks).7 Moreover, cortisol administration in an emergency unit setting is apparently able to prevent the development of PTSD.28 While these findings are promising, more research is needed to draw conclusions about the effectiveness, the underlying mechanisms, and long-term safety.

Stress and Multiple Memory Systems

In addition to its effect on memory quantity, stress also influences the quality of the memories formed.31 For example, spatial memory tasks can often be solved using either a cognitive map strategy dependent on the hippocampus or using a stimulus–response strategy dependent on the striatum. Stress influences the participation of multiple memory systems in the solution of a given memory task by reducing the contribution of hippocampus-based declarative memories. At the same time, striatum-based, implicit stimulus–response learning is unaffected or potentially even boosted.31 Interestingly, this shift appears to be mediated by the MR and is often able to rescue performance in the face of stress. A similar shift has been characterized during instrumental learning. Here, stress causes an increase in habitual behavior at the expense of PFC-mediated goal-directed behavior. As such, these shifts are typically adaptive since...
they may rescue performance at times when cognitive resources are compromised.\textsuperscript{31} However, in vulnerable individuals, these stress-induced shifts might promote the development of mental disorders such as addiction and obsessive compulsive disorder.\textsuperscript{30}

**STRESS AND COGNITION: CHRONIC EFFECTS**

The following paragraphs will focus on the impact of chronic stress on cognition. First, the long-term consequences of early life stress will be summarized. These changes have an impact throughout the lifespan leading up to old age. Next, the impact of chronic stress on memory in adulthood is reviewed.

**Early Life Stress and Its Long-Term Consequences**

There is mounting evidence to support the notion that early stress exposure is associated with accelerated neurodegenerative processes and early onset of memory decline in the course of aging.\textsuperscript{17} Changes in stress susceptibility programmed early on in life might partially account for such deficits.\textsuperscript{29}

Prenatal and postnatal stress exposure appears to be associated with a chronically increased reactivity of the HPA axis mediated by a reduced expression of central GRs.\textsuperscript{20} Animal models show increased corticosterone concentrations and lower GR density in the hippocampus in the offspring of stressed mothers. Also, postnatal maternal separation and poorer maternal care have been linked to reduced GR gene expression in the hippocampus, which, in turn, is associated with reduced feedback sensitivity of the HPA axis. Recently, an epigenetic mechanism has been discovered in rodents that explains how environmental stimuli can impact gene expression. Variation in maternal care during the first week of life was associated with differences in GR gene promoter DNA methylation, leading to stable changes in GR gene expression.\textsuperscript{41} Accumulating evidence suggests that the human GR gene is also influenced by early life programming.\textsuperscript{32} Apparently, individuals with an increased stress susceptibility (reflecting genetic susceptibilities and/or early adversity) are especially vulnerable to stress-induced cognitive impairments later on in their adult life.\textsuperscript{17}

**Cognitive Effects of Chronic Stress During Adulthood**

Animal research has provided important insights into the structural alterations caused by chronic stress in the brain. One main finding is that the integrity of the hippocampus and the medial PFC is compromised, while, in parallel, the amygdala (the “fear centre” of the brain) and parts of the striatum (the “habit centre” of the brain) become hyperactive.\textsuperscript{27} In the hippocampus, chronic stress leads to a retraction of dendrites (dendritic atrophy), and similar effects occur in the medial PFC.\textsuperscript{17} This atrophy appears to be reversible after stress termination, illustrating preserved room for neuroplasticity. In addition, stress causes reduced neurogenesis in the dentate gyrus and the mPFC. Even though the function of these new-born neurons is discussed controversially, a contribution to memory formation appears likely.\textsuperscript{36} At the behavioral level, impaired performance in hippocampus-dependent memory tasks and PFC-dependent tasks (e.g., working memory, goal-directed actions, set-shifting capabilities) can be observed.\textsuperscript{27}

In contrast to the hippocampus and the PFC, the amygdala becomes hypertrophic in conditions of chronic stress. Increases in dendritic arborization and spine density take place.\textsuperscript{27} Similar effects (dendritic hypertrophy) have been observed in the striatum.\textsuperscript{9} These alterations are summarized in Fig. 31.3. Moreover, CRF system activity in the amygdala, which is involved in anxiety, is enhanced. Chronically stressed animals show enhanced fear conditioning and are characterized by a more habitual and less goal-directed response style.\textsuperscript{9} Thus, the balance between brain regions involved in cognition is altered by chronic stress.\textsuperscript{17} While “analytic” cognitive functions mediated by the hippocampus and PFC are impaired, “affective” fear-related amygdala functioning and habit-related striatal functioning are enhanced.\textsuperscript{34}

In humans, exposure to chronic stress (e.g., shift workers, airplane personnel, soldiers) is associated with deficits in cognition such as working memory and declarative memory.\textsuperscript{17,34} These deficits can, in part, be explained by GC overexposure resulting from chronic stress. For example, several studies observed cognitive impairments after the administration of GCs over a period of several days. Further evidence comes from studies with patients receiving GC therapy for the treatment of autoimmune diseases. Whether the negative effects on memory reflect acute or chronic effects is sometimes hard to disentangle, and at least one study has shown a rapid reversal of the deficits after

**FIGURE 31.3** Effects of chronic stress on dendritic morphology. Three weeks of chronic stress causes dendritic atrophy in the hippocampus and medial PFC in rodents. In contrast, the amygdala and parts of the striatum become hypertrophic.
discontinuation of the GC treatment. Data from patients with Cushing disease point in the same direction, with cognitive impairments and hippocampal volume reductions reported. Hippocampal atrophy might be reversible once successful treatment has occurred. This would be in line with the remaining plasticity of this structure observed in rodent studies.

**INTERVENTION STRATEGIES**

In laboratory animals, stress-induced dendritic atrophy in the hippocampus and PFC as well as reduced neurogenesis in the hippocampus can be prevented with antidepressants and anticonvulsants. Also, treatment with a GR antagonist is effective in preventing such stress-induced changes in neurophysiology. Similarly, memory impairments can be prevented with some of these drugs.

In humans, chronic stress without an associated psychopathology could be alleviated by psychological stress intervention strategies. Possible examples are stress inoculation training or mindfulness-based stress reduction training. Initial evidence suggests that these psychological interventions can influence stress reponsivity and may even lead to structural alterations in the human brain.

Pharmacological treatment with beta blockers can prevent the effects of acute GC elevations on memory retrieval. It remains to be shown whether similar approaches are effective in conditions of chronic stress. In addition, GR antagonists and/or CRF antagonists might be candidate drugs. Moreover, drugs that influence the local GC metabolism in the brain could also be effective. For example, a pharmacological reduction of active GC concentrations in the hippocampus (inhibition of 11beta-HSD-1 synthesis) is efficient in preventing memory impairments in aging mice. In humans, a pilot study demonstrated that the 11beta-HSD-1 inhibitor carbenoxolone improved memory in older men and in patients with type 2 diabetes.

In MDD, pharmacological agents that normalize HPA axis activity are being tested, with CRF antagonists and GR antagonists being of particularly great interest. In addition to pharmacological approaches, there is initial evidence that HPRAxis dysfunction in MDD patients can be altered with the help of psychotherapy. This is of particular importance for patients who are known to respond less to pharmacotherapy, i.e., MDD patients with a history of early trauma.

In sum, reinstating appropriate HPA signaling appears to be a promising approach both in chronically stressed animals and in human patients suffering from stress-related mental disorders.

**OUTLOOK**

Research over the past decade has substantially helped to better understand the effects of GCs on memory. A more differentiated picture of stress effects on memory has evolved: oversimplifications in the form of statements such as “stress impairs memory” are no longer supported by the existing literature. An acute stress-induced GC increase enhances memory consolidation but impairs memory retrieval. These impairing effects of stress-induced GC secretion might prevent us from performing well during an exam and could also influence eyewitness testimonies. In addition, stress alters the quality of the memories formed.

Substantial sex differences have been observed in several animal studies, but evidence in humans is still sparse. The direction of the effect appears to be task specific. More knowledge about sex differences should, in the long run, help understand sex differences in stress-associated disorders. Future studies need to investigate whether these sex differences are related to differences in the neuroendocrine stress response or to differences in the brain’s response to endocrine stress messengers.

Chronic stress has mostly negative effects on both the brain and the body. These observations are relevant to mental disorders as well as to the aging process. However, it is encouraging that research has repeatedly observed evidence for preserved plasticity and structural remodeling once the stress has ceased or GCs are back to normal levels. Therefore, successful interventions will not only be able to stop the aggravation of symptoms but also should often be able to reverse the underlying pathological alterations.

**References**

REFERENCES


