Glucocorticoids and the regulation of memory in health and disease

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ABSTRACT

Over the last decades considerable evidence has accumulated indicating that glucocorticoids – stress hormones released from the adrenal cortex – are crucially involved in the regulation of memory. Specifically, glucocorticoids have been shown to enhance memory consolidation of emotionally arousing experiences, but impair memory retrieval and working memory during emotionally arousing test situations. Furthermore, growing evidence indicates that these different glucocorticoid effects all depend on emotional arousal-induced activation of noradrenergic transmission within the basolateral complex of the amygdala (BLA) and on interactions of the BLA with other brain regions, such as the hippocampus and neocortical regions. Here we review findings from both animal and human experiments and present an integrated perspective of how these opposite glucocorticoid effects might act together to serve adaptive processing of emotionally significant information. Furthermore, as intense emotional memories also play a crucial role in the pathogenesis and symptomatology of anxiety disorders, such as posttraumatic stress disorder (PTSD) or phobias, we discuss to what extent the basic findings on glucocorticoid effects on emotional memory might have implications for the understanding and treatment of these clinical conditions. In this context, we review data suggesting that the administration of glucocorticoids might ameliorate chronic anxiety by reducing retrieval of aversive memories and enhancing fear extinction.

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1. Introduction

Stress activates the hypothalamus–pituitary–adrenal axis, which results in the release of glucocorticoid hormones (cortisol in humans, corticosterone in rodents) from the adrenal cortex. It has long been recognized that glucocorticoids readily enter the brain and affect cognition. Early reports on both enhancing and impairing properties of glucocorticoids on memory [9,16,21,63,91] have indicated that these hormones have complex effects on cognitive functions. More recent studies investigating glucocorticoid effects on distinct memory phases and studies discerning acute from chronic effects helped to disentangle the multifaceted actions of these stress hormones. For example, acute elevations of glucocorticoids are known to enhance the consolidation of memory of new information, but to impair the retrieval of already stored information [51,146,156]. Conditions with chronically elevated glucocorticoid levels are usually associated with impaired cognitive performance and these deficits are thought to result from a cumulative and long-lasting burden on hippocampal function and morphology [102,172]. Recently, however, it became clear that memory deficits observed under such chronic conditions can also result, at least in part, from acute and reversible glucocorticoid actions on memory retrieval processes [39].

In the present review, we will summarize and discuss how glucocorticoids affect memory consolidation, retrieval and working memory and why these stress hormones specifically modulate memory of emotionally arousing experiences. Furthermore, because emotional memory plays a crucial role in the pathogenesis and symptomatology of anxiety disorders, such as posttraumatic stress disorder (PTSD) or phobias, we will discuss to what extent the basic findings on glucocorticoid effects on emotional memory might have clinical implications.

2. Glucocorticoid effects on memory consolidation

Memory consolidation is the process by which a fragile short-term memory trace is transferred into stable long-term memory. However, not all information is equally well transferred into long-term storage. In fact, it is well recognized that especially emotionally arousing experiences are well remembered, even after decades [107]. Successful memory consolidation depends on de-novo protein synthesis and on long-term changes in synaptic plasticity [76]. There is extensive evidence that glucocorticoids, along with other components of the stress response, are critically involved in regulating memory consolidation of emotionally arousing experiences [106]. Blockade of glucocorticoid production with
the synthesis inhibitor metyrapone impairs memory consolidation in both animals and humans [95,148] and prevents stress- or epinephrine-induced memory enhancement [90,149]. Acute systemic administration of glucocorticoids enhances long-term memory consolidation when given either before or immediately after a training experience [2,27,41,63,155,166,171]. Such glucocorticoid effects on memory consolidation follow an inverted U-shape dose–response relationship: Moderate doses enhance memory, whereas higher doses are typically less effective or may even impair memory consolidation [166]. In rodents, enhancing effects of glucocorticoids on memory consolidation have been observed in many different kinds of learning tasks, including inhibitory avoidance, contextual and cued fear conditioning, water-maze spatial and cued training, object recognition and conditioned taste aversion [161]. These findings indicate that, in animals, glucocorticoids not only enhance memory of training on hippocampus-dependent tasks that have a strong spatial/contextual component, but also memory of recognition- and procedural-training that are known to depend on other brain systems. In humans, glucocorticoid effects on memory consolidation have mostly been investigated with respect to declarative tasks [72,197].

Glucocorticoids also play a role in the consolidation of memory of extinction training. Extinction occurs when conditioned responding to a stimulus decreases when the reinforcer is omitted [139]. Like other forms of learning, extinction acquisition is followed by a consolidation phase and it has been found that the administration of glucocorticoids facilitates the consolidation of extinction memory, whereas a suppression of glucocorticoid function impairs such extinction processes [14,21,35,200]. Glucocorticoids have been shown to enhance memory consolidation and synaptic plasticity by influencing a wide variety of cellular functions, including cell signaling, ion channel properties as well as cell structure [20,78,145].

2.1. Role of emotional arousal in enabling glucocorticoid effects on memory consolidation

Recent findings suggest that glucocorticoids modulate memory consolidation of emotionally arousing experiences but do not affect memory consolidation of neutral information. Learning tasks in animal experiments are usually emotionally arousing because of the motivational stimulation necessary to elicit changes in behavior. We investigated the importance of emotional arousal in mediating glucocorticoid effects on memory consolidation in rats trained on an object recognition task [124]. Although no rewarding or aversive stimulation is used during object recognition training, such training induces modest novelty-induced stress or arousal [46]. However, extensive habituation of rats to the training apparatus (in the absence of any objects) prior to the training reduces the arousal level induced by object recognition training. We found that corticosterone administered systemically immediately after training enhanced 24-h retention performance of rats that were not previously habituated to the experimental context (i.e., emotionally aroused rats). In contrast, post-training corticosterone did not affect 24-h retention of rats that had received extensive prior habituation to the experimental context and, thus, had decreased novelty-induced emotional arousal during training [124] (Fig. 1).

A link between the level of emotional arousal at encoding and the efficacy of adrenocortical stress hormones in influencing memory consolidation has also been demonstrated in humans. Cortisol administered shortly before or after learning selectively enhances long-term memory of emotionally arousing, but not of emotionally neutral, items [27,86], but see [2]. Moreover, a cold pressor stress in humans (i.e., placing the arm in ice water for up to 3 min), a procedure that significantly elevates endogenous cortisol levels, enhances memory of emotionally arousing slides, but does not affect memory of relatively neutral slides [32]. Consistent with these findings, it has been reported that levels of endogenous cortisol at the time of learning correlated with enhanced memory consolidation only in individuals who were emotionally aroused [3]. Furthermore, it has been found that a stress-induced elevation of cortisol levels was associated with enhanced consolidation of emotionally arousing memory of conditioned fear [210]. Thus, these findings from animal and human studies indicate that training-associated endogenous emotional arousal is essential for enabling glucocorticoid effects on memory consolidation.

2.2. Role of arousal-induced noradrenergic activation in the amygdala

Why do stress hormones selectively enhance memory consolidation of emotionally arousing experiences? Our findings suggest that interactions between stress hormones and amygdala activity may be key in determining this selectivity. It is well established that emotional experiences that induce the release of adrenal stress hormones also activate the amygdala [36,129]. Evidence from a large number of studies in both animals and humans has indicated that the amygdala plays a critical role in a variety of processes involving emotionally arousing information, including emotional influences on attention, perception, and learning and memory [89,130]. Extensive evidence from our as well as other laboratories indicates that the enhancing effects of stress hormone administration on the consolidation of memory of emotionally arousing experiences involve the amygdala. Lesions of the basolateral complex of the amygdala (BLA) block the memory-modulatory effects induced by post-training systemic injections of glucocorticoids [105,155]. As lesions of the adjacent central nucleus of the amygdala (CEA) are ineffective, the BLA appears to be the critical region of the amygdala in mediating stress and arousal effects on memory consolidation. Moreover, and in support of this view, post-training infusions of a specific glucocorticoid receptor (GR) agonist administered into the BLA, but not the CEA, enhance memory consolidation, whereas intra-BLA infusions of a GR antagonist impair memory consolidation or block the facilitatory effects of stress exposure [40,59,158]. These findings thus indicate that the BLA may be a critical gateway in mediating stress hormone effects on memory consolidation.

In addition, there is evidence that glucocorticoids require noradrenergic activation within the BLA to influence memory of emotionally arousing training. In vivo microdialysis experiments in rats have shown that electric footshock, or training on an inhibitory avoidance task, induces the release of norepinephrine in the amygdala [67,108,136]. A blockade of the β-adrenoceptor or of
Based on the evidence summarized above, it may be hypothesized that emotional arousal-induced increases in noradrenergic activity within the BLA are essential in enabling glucocorticoid hormone effects on memory consolidation. Such a mechanism may then provide a direct explanation of the findings that glucocorticoid hormones selectively enhance memory consolidation of emotionally arousing experiences. We recently investigated this issue in rats trained on an object recognition task. As is discussed above, corticosterone enhances memory of object recognition training when administered to naive rats, but is ineffective in rats that have reduced training-associated emotional arousal because of prior habituation to the experimental context [124]. We found that, in non-habituated (i.e., emotionally aroused) rats, the β-adrenoceptor antagonist propranolol blocked the corticosterone-induced memory enhancement [162]. Propranolol infused directly into the BLA also blocked the enhancing effects of corticosterone on object recognition memory. To determine whether the failure of corticosterone to enhance memory consolidation under low-arousing conditions is due to insufficient training-induced noradrenergic activation, low doses of the α2-adrenoceptor antagonist yohimbine, which increases norepinephrine levels in the brain, were co-administered with the corticosterone to well-habituated rats immediately after object recognition training. The critical finding of this study was that such an augmented noradrenergic tone was sufficient to mimic the effects of emotional arousal in that simultaneously administered corticosterone enhanced memory consolidation [162]. Further, in habituated rats, corticosterone activated BLA neurons, as assessed by phosphorylated cAMP response-element binding (pCREB) protein immunoreactivity levels, only in animals also given yohimbine. Such observations strongly suggest that because glucocorticoid effects on memory consolidation require noradrenergic activation within the BLA, they only modulate memory under emotionally arousing conditions that induce the release of norepinephrine.

Human studies have also provided evidence that stress hormone effects on memory enhancement for emotionally arousing experiences require amygdala activity. Memory for emotionally arousing material is not enhanced in human subjects with selective...
bilateral damage to the amygdala, as it is in normal subjects [5,31]. Studies using brain positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) techniques have provided evidence that amygdala activity during viewing of emotionally arousing stimuli correlates highly with the subjects’ recall of the material assessed weeks later [33,37,70]. Furthermore, the relationship between amygdala activity during encoding and subsequent memory was greatest for the material rated as being the most emotionally intense. In a recent study it has been shown that amygdala activity during viewing of emotionally arousing pictures was greatest for those subjects who responded with a large increase in endogenous cortisol [193] and the combination of pharmacologically induced elevation of central norepinephrine and cortisol in healthy subjects produced a negative response bias in the amygdala [87]. Furthermore, a β-adrenoceptor antagonist blocked the increase in amygdala activity and the enhanced retention induced by either emotional arousal or endogenous cortisol [34,188,194].

2.3. Interaction of the amygdala with other brain regions

As indicated, glucocorticoids are known to enhance memory consolidation of training on many different kinds of emotionally arousing tasks, including inhibitory avoidance, contextual and cued fear conditioning, water-maze spatial and cued training, object recognition and conditioned taste aversion. As these different training experiences are known to engage different brain systems during both training and the consolidation occurring after training [69,73,128], the stress hormone-induced modulation involves receptor activation in a variety of brain regions. For example, glucocorticoids administered into the hippocampus influence memory of water-maze spatial training [157], which is consistent with a role of the hippocampus in spatial/contextual learning and memory [96,118,169]. Glucocorticoids infused into the hippocampus also enhance memory of inhibitory avoidance training [157]. In fear conditioning tasks, including inhibitory avoidance, the rats learn that footshock occurs in a specific context. Importantly, lesions of the BLA or the administration of a β-adrenoceptor antagonist into the BLA block the enhancing effect of post-training intra-hippocampal infusions of a GR agonist on inhibitory avoidance memory [157,160]. BLA lesions also block the impairing effect of a GR agonist infused into the hippocampus on spatial memory in water-maze [157]. Thus, these findings indicate that an intact and functional BLA is required for enabling memory modulation of spatial/contextual information induced by manipulation of GR activity in the hippocampus. Importantly, corticosterone enhances memory consolidation of conditioned taste aversion when infused post-training into the insular cortex or the BLA, but is ineffective when administered into the hippocampus, a region that does not play a significant role in taste learning [116]. Other findings suggest that corticosterone infusions into the caudate nucleus may selectively modulate the consolidation of memory of implicit (i.e., stimulus response) forms of learning [109] and there is evidence that BLA activity also regulates insular cortex- and caudate nucleus-dependent memory consolidation [115,127]. Taken together, these findings indicate that glucocorticoids act in different brain regions to enhance the consolidation of different aspects of information acquired during training. Although the BLA plays a critical role in regulating stress hormone effects on memory consolidation, extensive evidence indicates that it is not a permanent storage site of such memory traces [105], but rather interacts with these other brain regions in regulating memory consolidation of different kinds of information [104].

A growing body of evidence indicates that BLA neuronal activity is closely regulated by the medial prefrontal cortex (mPFC) [43,68,138]. The mPFC is primarily involved in higher-order cognitive functions such as thought, decision-making and working memory [61,140] and exerts a strong inhibitory (i.e., fear-reducing) influence on behaviors [7]. Stress exposure is known to impair this mPFC-dependent inhibitory control [94] and to block long-term potentiation in the BLA–mPFC pathway [98]. We found that post-training infusions of a GR agonist administered into the mPFC enhanced memory consolidation of inhibitory avoidance training (Roozendaal et al., unpublished observation). In support of the view that a GR agonist administered into the mPFC enhances memory consolidation via a top–down regulation of BLA activity [100,167], the GR agonist infused into the mPFC after inhibitory avoidance training, but not in non-trained rats, increased BLA levels of phosphorylated extracellular signal-regulated kinase 1/2 (pErk1/2). Blockade of this pErk1/2 activity in the BLA prevented the memory enhancement induced by intra-mPFC administration of the GR agonist. Thus, these findings suggest that GR activation within the mPFC may enhance memory consolidation via a stimulatory influence on BLA activity, i.e., a loss of inhibitory control.

3. Glucocorticoid effects on memory retrieval

Studies showing that stress induces memory impairment when retention is tested shortly after learning (before memory consolidation took place) and glucocorticoid levels are still elevated [54,81], indicated that glucocorticoids possibly interfere with memory retrieval processes. In the first study investigating the specific effects of stress and glucocorticoids on memory retrieval [51], we reported that 30 min after exposure to footshock stress, rats had impaired retrieval of spatial memory of a water-maze task they had acquired 24 h earlier. Interestingly, memory performance was not impaired when rats were tested either 2 min or 4 h after the footshock. These time-dependent effects on retrieval processes corresponded to the circulating corticosterone levels at the time of testing, which suggested that the retrieval impairment was directly related to increased adrenocortical function. In support of this idea, we found that suppression of corticosterone synthesis with metyrapone blocked the stress-induced retention impairment. In addition, systemic corticosterone administered to non-stressed rats 30 min before retention testing induced dose-dependent retention impairment. Because similar footshock stress or corticosterone administration did not affect acquisition or immediate recall on the water-maze task, the corticosterone-induced impairment in retention performance is likely attributable to a selective influence on memory retrieval. In a next step, we have translated these findings to healthy humans and found that a single administration of 25 mg cortisol impaired the recall of words learned 24 h earlier [52]. Several further studies from different laboratories have indicated that glucocorticoids impair memory retrieval of spatial or contextual memory in rats and declarative (mostly episodic) memory in humans [29,39,49,72,83,142,152,153,170,197,198]. Moreover, increased cortisol levels after psychological stress exposure have also been shown to impair declarative memory retrieval [28,58,84].

The memory retrieval impairment induced by a single administration of glucocorticoids appears to be of temporary nature. Corticosterone injection impairs the acute retrieval of contextual fear memory without affecting retrieval performance 48 h later [35]. However, one study reported that a single administration of glucocorticoids not only induces acute, but also prolonged impairment of memory retrieval in humans [190]. In that study, subjects were asked to retrieve previously learned information after ingestion of 35 mg cortisol or placebo. The single administration of cortisol induced an acute impairment in memory recall, which, however, was still observed in an additional recall test after a 1-week washout period. The persistence of this retrieval impairment might be due...
to a reduced rehearsal during retrieval under treatment and hence a lower re-encoding of the retrieved material. Alternatively, cortisol might have inhibited memory reconsolidation processes (see discussion under Section 5.4).

An important question is whether glucocorticoid effects on memory retrieval occur only under acutely elevated glucocorticoid levels or also under chronic conditions. There is substantial evidence that sustained endogenous hypercortisolemia, such as found in depression, Cushing’s disease or human aging, is often associated with declarative memory impairment [92,168,179,186]. Moreover, prolonged glucocorticoid therapy, which is widely used in clinical practice, is known to induce cognitive deficits [18,24,25,79,199]. Although considerable evidence suggests that long-term glucocorticoid exposure may cause cognitive impairment via cumulative and long-lasting influences on hippocampal function and morphology [24,74,102,172,186], it is possible that also acute hormonal influences on retrieval processes contribute to the memory deficits found with chronic glucocorticoid exposure. To investigate this question, we recently examined memory functions and hippocampal volume in patients with rheumatoid arthritis who were treated either chronically (i.e., for a mean duration of 5 years) with low to moderate doses of prednisone or without glucocorticoids. In both groups, delayed recall of words learned 24 h earlier was assessed under conditions of either elevated or basal glucocorticoid levels in a double-blind, placebo-controlled crossover design. The findings did not indicate harmful effects of a history of chronic prednisone treatment on memory performance or hippocampal volume (i.e., no differences between both groups were found when retention was tested under placebo treatment). However, we found evidence that acute prednisone administration 1 h before retention testing to either the steroid or non-steroid group impaired verbal recall [39]. Thus, these findings indicate that acute and reversible effects of glucocorticoids on retrieval processes contribute to the memory deficits found in conditions of chronically elevated glucocorticoid levels.

3.1. Role of arousal-induced noradrenergic activation in enabling glucocorticoid effects on memory retrieval

Glucocorticoid effects on memory retrieval are highly comparable to those seen in studies investigating memory consolidation in that the effects depend on emotional arousal. Specifically, it has been shown in recent studies in humans that emotionally arousing information is especially sensitive to the retrieval-impairing effects of glucocorticoids (Fig. 3) [48,83,84,182], but see [190], and that emotional arousal during the test situation enables glucocorticoid effects on memory retrieval [85]. Studies of rats investigating the neural mechanisms underlying this selectivity have indicated that glucocorticoid effects on memory retrieval depend critically on noradrenergic activity within the brain. Systemic administration of the β-adrenoceptor antagonist propranolol blocks the memory retrieval impairment of spatial/contextual information induced by a concurrent injection of corticosterone [151]. A β-adrenoceptor antagonist infused into the hippocampus also prevents the retrieval-impairing effect of a GR agonist administered concurrently [153]. As stimulation of β1-adrenoceptors with systemic injections of the selective agonist xamoterol induces memory retrieval impairment comparable to that seen after corticosterone administration [153], the findings suggest that glucocorticoid effects on memory retrieval impairment involve a facilitation of noradrenergic mechanisms. Together with the finding that norepinephrine is activated by emotional arousal, this could explain why emotionally arousing information or an emotionally arousing test situation is a prerequisite for enabling glucocorticoid effects on memory retrieval. In line with this idea, we recently reported that the β-adrenoceptor antagonist propranolol blocked the impairing effect of cortisone on the retrieval of emotionally arousing verbal material in healthy humans [Fig. 3] [48]. These findings may have important clinical implications as β-adrenoceptor antagonists might prove useful for the prevention of glucocorticoid-induced memory deficits in acute stressful situations [84], as well as for the treatment of memory deficits in conditions associated with chronically elevated glucocorticoid levels, such as depression or medical conditions requiring glucocorticoid treatment [39,150].

3.2. Role of amygdala–hippocampal interaction in enabling glucocorticoid effects on memory retrieval

Extensive evidence from studies in amnesic patients, human imaging studies, and lesion studies in animals indicates that the medial temporal lobe (hippocampus and parahippocampal gyrus) is crucially involved in memory retrieval of spatial and contextual memory in animals and declarative memory in humans [30,119,185]. Systemic administration of glucocorticoids to rats shortly before retention testing induces memory retrieval impairments for contextual and spatial memory [51,151]. Furthermore, we found that local infusions of a GR agonist into the hippocampus of rats induce retrieval impairment on a water-maze spatial task comparable to that seen after systemic administration [152]. In parallel, we performed a PET study in healthy humans and found that acutely administered cortisone reduces blood flow in the medial temporal lobe during memory recall of words, an effect that correlated with the degree of memory retrieval impairment [49]. Moreover, a recent fMRI study found that glucocorticoids decrease hippocampal and prefrontal activation during declarative memory retrieval [121]. Further studies in animals have indicated that the BLA interacts with the hippocampus in mediating glucocorticoid effects on the retrieval of emotionally arousing information. Lesions of the BLA or the infusion of a β-adrenoceptor antagonist into the BLA block the impairing effect of a GR agonist infused into the
hippocampus on memory retrieval of spatial information [152, 153]. In support of the importance of an interaction between the amygdala and the hippocampus during retrieval of emotionally arousing information, human imaging studies have indicated that the degree of interaction between these two brain regions is greater during the retrieval of emotionally arousing declarative information as compared to neutral information [57,183]. Therefore, comparable to the glucocorticoid effects on memory consolidation, the amygdala interacts with the hippocampus in mediating glucocorticoid effects on the retrieval of hippocampus-dependent memory.

4. Glucocorticoid effects on working memory

Working memory is a dynamic process whereby information is updated continuously, providing a temporary storage of information [12,75]. Evidence from lesion, pharmacological, imaging and clinical studies indicates that working memory depends on the integrity of the prefrontal cortex [23,66,126]. Stress exposure is known to impair performance of rats on a delayed alternation task, a task commonly used to assess working memory in rodents [11]. Basal levels of endogenous glucocorticoids are required to maintain prefrontal cortical function [117], but systemic injections of stress doses of corticosterone or administration of the GR agonist RU 28362 into the mPFC impair delayed alternation performance in rats [159]. As similar GR agonist infusions into the mPFC do not impair delayed alternation performance on non-mnemonic control tasks that have similar motivational and motor demands (Barsegyan and Roozendaal, unpublished observation), these findings strongly suggest that glucocorticoids, via GR activation, impair working memory. Additionally, stress or stress-level cortisol treatment is known to impair working memory performance in human subjects during demanding tasks that require a high level of arousal [12,93,178,198,208]. Importantly, like glucocorticoid effects on memory consolidation and retrieval, these hormones interact with noradrenergic mechanisms in inducing working memory impairment. A β-adrenoceptor antagonist administered systemically blocks the impairing effect of corticosterone on working memory in rats [159]. Furthermore, a β-adrenoceptor antagonist or cAMP blocker infused into the mPFC also blocks working memory impairment induced by a GR agonist administered concurrently (Barsegyan and Roozendaal, unpublished observation). Animal studies have shown that glucocorticoid effects on working memory also depend on functional interactions between the BLA and the mPFC. Disruption of BLA activity blocks the effect on working memory of a GR agonist administered into the mPFC [159]. This evidence provides strong support for the hypothesis that BLA activity modulates stress and emotional arousal effects on working memory in other brain regions.

5. Modulatory effects of glucocorticoids on emotional memory: implications for anxiety disorders

From the findings reviewed above we have learned that glucocorticoids enhance memory consolidation but impair memory retrieval and working memory in emotionally arousing situations (Fig. 4). Enhanced memory for emotional events is a well-recognized phenomenon, which helps us to remember important information. Although glucocorticoid-induced temporary impairments of memory retrieval and working memory are certainly unwanted in exam situations, these effects should not a priori be regarded as maladaptive. In fact, these effects may actually aid to an accurate storage of emotionally arousing information by blocking, for example, retroactive interference [147]. However, whereas the enhanced memory for emotionally arousing events in most cases has a clear adaptive value, in certain circumstances extremely arousing experiences can also lead to highly emotional, traumatic or fearful memories, which contribute to the development and symptoms of anxiety disorders. Therefore, understanding the basic modulatory actions of glucocorticoids on different aspects of cognition may have important implications for understanding and, possibly, treating anxiety disorders. Although we focus in this paper on the implications of memory-modulatory glucocorticoid effects for anxiety disorders, these glucocorticoid effects are likely to have important implications for other psychiatric disorders, such as depression or schizophrenia, as well [17,120,168,187].

5.1. The role of aversive memories in anxiety disorders

Several lines of evidence indicate that after an aversive experience the formation of an aversive memory trace is an important pathogenic mechanism for the development of anxiety disorders, such as PTSD or phobias [89,114,130,131,205]. Neuroimaging studies have shown that while the prefrontal cortex seems to be hypo-responsive, amygdala activity in response to viewing aversive information is exaggerated in patients with PTSD as compared to healthy controls and, importantly, correlates positively with later recall of the aversive information, and with PTSD symptom severity [10,56,65,71,143,180,181]. These findings are in line with the well-known role of the amygdala in the formation of emotional memory, as reviewed above. Furthermore, some evidence indicates that the administration of a β-adrenoceptor blocker, which is known to reduce the consolidation of memory of emotionally arousing experiences, might be preventive with regard to the development of subsequent PTSD [134]. These findings underscore the important pathogenic role of aversive memory formation in the development of PTSD. However, the formation of a strong aversive memory trace is of course not sufficient to develop an anxiety disorder. In fact, building strong memories of an aversive event is a primarily adaptive mechanism and even intrusive thoughts (intrusive memory retrieval) and related symptoms are normal reactions in the first period after an aversive experience. In individuals who do not develop an anxiety disorder, which fortunately is mostly the case, intrusive memory retrieval declines over time, although the aversive memory can still be recalled voluntarily even after a long time. In contrast, in individuals who do develop a chronic anxiety disorder, the aversive memory trace remains easily reactivatable by an aversive cue (e.g. trauma cue or phobic stimulus), or even spontaneously, leading to uncontrollable aversive memory retrieval and related clinical symptoms (re-experiencing in PTSD, fear in phobia).

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PTSD is a chronic response to a traumatic event and characterized by the following features: re-experiencing of the traumatic event, avoidance of stimuli associated with the trauma, and hyperarousal. Re-experiencing symptoms include intrusive daytime recollections, traumatic nightmares and flashbacks in which components of the event are relived [8,202]. These re-experiencing symptoms result from excessive retrieval of traumatic memories which often retain their vividness and power to evoke distress for decades or even a lifetime. Importantly, traumatic re-experiencing phenomena are again consolidated (re-consolidated) into memory, which cements the traumatic memory trace (see the discussion of the concept of intrusions in the PTSD research literature, e.g. [22,112,113]). Persistent retrieval, re-experiencing and re-consolidation of traumatic memories is a process that keeps these memories vivid and thereby the disorder alive (see Section 5.4).

Phobic disorders are characterized by marked and persistent fear that is excessive or unreasonable, cued by the presence or anticipation of a specific object or situation [8,13,97]. Exposure to a phobic stimulus almost invariably provokes retrieval of stimulus-associated fear memory which leads to the fear response [42,64,88]. In addition, phobic individuals tend to construct highly negative images of a phobic situation, which substantially contribute to anticipatory anxiety as well as negative postevent processing. Such images are usually associated with explicit fearful memories of past phobic experiences which reinforce negative beliefs that are difficult to suppress and may strengthen the phobic response [60,141]. Thus, retrieval of aversive memories (traumatic memory in PTSD and fear memory in phobias) plays an important role in the symptomatology of these anxiety disorders.

5.2. Glucocorticoids and PTSD

5.2.1. Preventive effects of glucocorticoids with regard to the development of PTSD

From the basic studies discussed above, we have learned that acutely elevated glucocorticoids enhance the consolidation of emotional memories. Based on these findings, it can be assumed that elevated glucocorticoid levels at the time of an aversive experience may contribute to the formation of traumatic and fearful memories. This idea is supported by a recent study on traumatic memories in critically ill patients. These patients often report traumatic memories from intensive care treatment and have a relatively high incidence of chronic stress symptoms and PTSD during follow-up [176]. We found that the number of traumatic memories from the intensive care unit correlated positively with the amount of cortisol acutely administered to patients undergoing cardiac surgery [175]. Theoretically, it might therefore be useful to therapeutically block glucocorticoid signaling immediately after a traumatic incident, as has been proposed for adrenergic signaling [132]. However, to block initial consolidation of aversive memories, the anti-glucocorticoid treatment should be given shortly after the aversive event. This is usually not possible and therefore this approach seems difficult. Moreover, there is evidence suggesting that reduced cortisol excretion in response to a traumatic event is actually associated with an increased risk of developing subsequent PTSD [53,103,206]. These findings suggest that elevated glucocorticoid levels after an aversive event might be preventive with regard to the development of PTSD. This idea is strongly supported by studies showing that prolonged (several days) administration of stress doses of cortisol during intensive care treatment reduces the risk for later PTSD [173,174,177,196]. But how do such findings of preventive effects fit with the idea that glucocorticoids enhance the formation of traumatic memories? After initial consolidation of traumatic experiences, which is likely to be enhanced by glucocorticoids, cortisol levels later on may play a crucial role in controlling the amount of retrieved traumatic memories. Specifically, by the known reducing effects of glucocorticoids on memory retrieval, high levels of these hormones may partly interrupt the vicious cycle of retrieving, re-experiencing and re-consolidating aversive memories, thereby preventing a further cementation of the aversive memory trace. Studies showing that the preventive effects of glucocorticoid administration are also observed when the treatment started already at the time of the traumatic event [174,196] indicate that such an inhibitory effect of glucocorticoids on memory retrieval prevails the potentially enhancing effect on initial consolidation. Taken together, these findings suggest that elevated glucocorticoid levels (endogenously or pharmacologically) act preventively with regard to the development of PTSD.

5.2.2. Glucocorticoids reduce the retrieval of traumatic memories in chronic PTSD

In addition to individuals at risk for PTSD, also patients with an established PTSD can show low endogenous cortisol levels [19,99,201,203,204,207], but see [133,209]. A recent meta-analysis has shown that low cortisol levels depend on several factors, including gender and trauma type [110]. Low cortisol levels may contribute to a hyper-retrieval of aversive memories. Based on the finding that glucocorticoids impair the retrieval of emotional information, we hypothesized that patients with chronic PTSD might benefit from glucocorticoid treatment. In an initial study, we tested this hypothesis in a small number of patients with chronic PTSD [6]. During a 3-month observation period, low-dose cortisol (10 mg per day) was administered orally for 1 month using a double-blind, placebo-controlled, crossover design. The administration of this low dose of cortisol for 1 month does not cause major side effects and does not suppress endogenous cortisol production [38]. To assess possible treatment effects on the retrieval of traumatic memories, the patients rated daily the intensity and frequency of the feeling of reliving the traumatic event and the physiological distress felt in response to traumatic memories and nightmares (self-administered rating scales from the Clinician Administered PTSD Scale questions). The results of this study indicated that low-dose cortisol treatment had beneficial effects with regard to re-experiencing symptoms and nightmares and we found evidence for cortisol effects that outlasted the treatment period [6].

5.3. Glucocorticoids reduce fear in phobia

In recent clinical studies we found evidence that glucocorticoids may not only have beneficial effects in patients with PTSD but also in patients with phobias. We administered glucocorticoids to 40 subjects with social phobia and 20 subjects with spider phobia in two double-blind, placebo-controlled studies [184]. In the social phobia study, cortisolone (25 mg) administered orally 1 h before a socio-evaluative stressor (Trier Social Stress Test [55,80]) significantly reduced self-reported fear during the anticipation-, exposure-, and recovery-phase of the stressor (Fig. 5A). Moreover, the stress-induced release of cortisol in placebo-treated subjects correlated negatively with fear ratings, suggesting that endogenously released cortisol in the context of a phobic situation buffers fear symptoms. This finding also indicates that reduced fear after glucocorticoid administration was not the result of a negative feedback on corticotropin-releasing factor (CRF) release.

In the spider phobia study, repeated oral administration of cortisol (10 mg), but not placebo, 1 h before exposure to a spider photograph induced a progressive reduction of stimulus-induced fear (Fig. 5B). This effect was maintained when subjects were exposed to the stimulus again 2 days after the last cortisol administration, suggesting that cortisol also facilitated the extinction of phobic fear (Fig. 5B). As in phobias retrieval processes cannot be measured directly, it cannot be ruled out that cortisol, perhaps in addition to influencing memory retrieval, may have reduced fear by exerting...
Adapted from Soravia et al. [184]. Fears ratings are depicted as mean ± SEM. Photograph), whereas no pharmacological treatment was given in sessions 1 and 6. Cortisol (10 mg) or placebo 1 h before exposure to the phobic stimulus (spider) induced fear in spider phobia. In sessions 2–5, subjects were administered either cortisol administration can influence the startle reflex [26] and reduce preconscious attention to fear in anxious young men [135]. However, in these studies cortisol did not affect subjective fear levels. In addition, in the phobia study, glucocorticoid administration did not affect phobia-unrelated anxiety, mood, wakefulness, or calmness, suggesting that glucocorticoids did not reduce phobic fear by general anxiolytic effects [184]. Moreover, recent findings indicating that acute cortisol elevations cause heightened arousal ratings of neutral stimuli [1] make a general or direct anxiolytic effect of glucocorticoids unlikely.

5.4. Possible mode of action of glucocorticoids in the reduction of aversive memory

The results of our clinical studies suggest that glucocorticoid administration induces acute effects on clinical symptoms by reducing the retrieval of aversive memories, i.e., traumatic memory in PTSD [6] and fear memory in phobia [184]. Additionally, in both studies we found evidence that symptoms were reduced even after cessation of the treatment period. What might be the underlying mechanism? Let us first review the processes which contribute to the persistence of these disorders: In PTSD, excessive retrieval of traumatic memory, which may be spontaneous or triggered by a trauma cue, leads to re-experiencing of the traumatic event [111]. In phobia, retrieval of fear memory triggered by a fear cue (phobic situation or object) leads to a fear response. (Re)consolidation of such aversive experiences further cements the aversive memory trace and thereby contributes to the persistence of these disorders (Fig. 6A). By inhibiting memory retrieval, cortisol may partly interrupt the vicious cycle of spontaneous retrieving, re-experiencing and reconsolidating traumatic memories in PTSD and, thereby, promote forgetting, a spontaneous process that occurs when memory is not reactivated (Fig. 6B). Furthermore, cortisol may facilitate the extinction of aversive memories, as evidenced by animal studies showing that glucocorticoid signaling promotes memory extinction processes [14, 21, 200]. Glucocorticoids may facilitate extinction in two ways: (i), because of the cortisol-induced reduction of memory retrieval, an aversive cue is no longer followed by the usual aversive memory retrieval and related clinical symptoms but, instead, becomes associated with a non-aversive experience which is stored as extinction memory; (ii), because elevated glucocorticoid levels are known to enhance the long-term consolidation of memories [27, 63, 82, 86, 146], it is possible that glucocorticoids facilitate the storage of corrective experiences. This is supported by recent animal studies showing that postretrieval administration of glucocorticoids is able to enhance the consolidation of extinction memory [4, 35]. Theoretically, such postretrieval (or postreactivation) glucocorticoid effects may also be interpreted as an inhibition of reconsolidation [192, 195]. However, findings in animals suggest that reconsolidation of aversive memory is disrupted by blocking rather than by activating glucocorticoid signaling [191]. Furthermore, in favor of the memory extinction hypothesis, it has been shown that postretrieval effects of glucocorticoids on memory are of transient nature and are reversed by a reminder, but see [195], which should not occur after inhibited reconsolidation. Although the data currently available rather speak for a facilitating effect of glucocorticoids on memory extinction, it is possible that, perhaps under certain conditions, glucocorticoids may also inhibit memory reconsolidation processes.

6. Conclusion

In the present paper we have reviewed evidence from both animal and human studies, which indicated that glucocorticoids enhance memory consolidation but impair memory retrieval and working memory (Fig. 4). Importantly, these hormone effects depend on emotional arousal-induced activation of noradrenergic transmission within the BLA and on interactions of the BLA with other brain regions, such as the hippocampus and neocortical regions. Therefore, glucocorticoids, via BLA activation, can modulate memory processes of many different kinds of emotionally arousing experiences.
Enhanced consolidation of emotionally arousing information is an adaptive mechanism, which helps us to retain important information. Reduced memory retrieval and working memory should not a priori be regarded as maladaptive as they support this process of retaining important information. In addition, the reduction of memory retrieval may aid to suppressing behaviors that are no more relevant or even maladaptive. This mechanism is especially important in more chronic situations when the organism is forced to adapt to a changed environment (e.g. environmental disaster, war). Under such conditions, also the facilitating effects of glucocorticoids on extinction processes represent an adaptive response, which helps the organism to deal with stressful events [47,101].

Because emotionally aversive memories play an important role in the development and symptomatology of anxiety disorders, we aimed to translate the basic findings on the effects of glucocorticoids on emotional memory in animals and healthy humans to clinical conditions. Specifically, the findings, which indicated that glucocorticoids reduce memory retrieval and enhance extinction of emotional memories led us to hypothesize that these stress hormones might be useful in the treatment of anxiety disorders. Clinical studies and studies of animal models of acquired fear indicate that glucocorticoid treatment indeed reduces the retrieval of traumatic memories and enhances extinction processes. These dual actions of glucocorticoids seem to be especially suited for the

**Fig. 6.** Model on the role of glucocorticoids in the reduction of aversive memory: (A) excessive retrieval of aversive memories causes re-experiencing symptoms in PTSD and phobic fear in phobia. Reconsolidation of such aversive experiences further cements the aversive memory trace and (B) glucocorticoid-induced reduction of the aversive memory trace. By inhibiting memory retrieval, glucocorticoids partly interrupt this vicious cycle of retrieving (1), re-experiencing (2) and reconsolidating (3) aversive memories, which leads to a weakening of the aversive memory trace (4). Furthermore, because the aversive cue is no longer followed by the usual aversive memory retrieval and related clinical symptoms, the cue becomes associated with a non-aversive experience, which is stored as extinction memory (5). Based on the findings of animal studies, glucocorticoids are likely to enhance long-term consolidation of extinction memory (see text for details).
treatment of acquired fear. By inhibiting memory retrieval, glucocorticoids may partly interrupt the vicious cycle of spontaneous retrieving, re-experiencing and (re)consolidating aversive memories. Furthermore, by enhancing extinction processes, glucocorticoids facilitate the storage of corrective experiences. Therefore, the combination of glucocorticoids with exposure techniques in cognitive-behavioral therapy may be a promising approach.

Future research should include large-scale clinical studies to evaluate the therapeutic efficacy of glucocorticoids in the treatment of anxiety disorders and to explore the efficacy of combining glucocorticoid treatment with psychotherapy. More research is also needed to better understand the molecular underpinnings of glucocorticoid actions on different memory processes as well as the role of (epi)genetic differences across individuals [50]. Such research might further promote the understanding of why some individuals become vulnerable to anxiety disorders, whereas others are resilient or even gain strength from stressful experiences.

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