Journal of Neuroendocrinology

Journal of Neuroendocrinology, 2016, **28**, 10.1111/jne.12353

REVIEW ARTICLE

Stress and Memory: A Selective Review on Recent Developments in the Understanding of Stress Hormone Effects on Memory and Their Clinical Relevance

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Journal of Neuroendocrinology

Stress causes a neuroendocrine response cascade, leading to the release of catecholamines and glucocorticoids (GCs). GCs influence learning and memory by acting on mineralocorticoid (MR) and glucocorticoid (GR) receptors. Typically, GCs enhance the consolidation of memory processing at the same time as impairing the retrieval of memory of emotionally arousing experiences. The present selective review addresses four recent developments in this area. First, the role of the endocannabinoid system in mediating the rapid, nongenomic effects of GCs on memory is illustrated in rodents. Subsequently, studies on the impact of the selective stimulation of MRs on different memory processes in humans are summarised. Next, a series of human experiments on the impact of stress or GC treatment on fear extinction and fear reconsolidation is presented. Finally, the clinical relevance of the effects of exogenous GC administration is highlighted by the description of patients with anxiety disorders who demonstrate an enhancement of extinction-based therapies by GC treatment. The review highlights the substantial progress made in our mechanistic understanding of the memory-modulating properties of GCs, as well as their clinical potential.

Key words: glucocorticoids, cortisol/corticosterone, mineralocorticoids, aldosterone, norepine phrine, receptors, membrane/nuclear

doi: 10.1111/jne.12353

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Introduction

The stress-induced activation of the hypothalamic-pituitary-adrenal (HPA) axis and the release of glucocorticoid (GC) hormones (cortisol in humans; corticosterone in rodents) is of crucial importance for adaptation to stress, in part through their effects on learning and memory via modulation of mineralocorticoid (MR) and glucocorticoid (GR) receptors (1–3). Although the effects of stress on memory have obvious adaptive value in evolutionary terms in that it is vital to remember both dangerous and favourable situations (4), in some circumstances, these influences might underlie memory distortions in stress-associated mental disorders (5). At the same time, there is mounting evidence that the memory-modulating properties of stress hormones might be beneficial for the prevention (6) or treatment of anxiety disorders (see below).

Stress and GCs exert phase-dependent effects on long-term memory, with enhancing effects on the consolidation of memory and impairing effects on memory retrieval (7–9). Studies in rodents have clarified the underlying mechanisms. Stress first results in a rapid activation of the sympathetic nervous system and the release of epinephrine from the adrenal medulla, which leads via stimulation of β-adrenoceptors on the vagus nerve to an enhanced release of norepinephrine in the basolateral complex of the amygdala (BLA). This initial arousal signal within the BLA interacts with the delayed GC signal in modulating memory in other brain regions, such as the hippocampus and neocortex (4). Permanent disruption of BLA activity, as well as β-adrenoceptor antagonist infusions into the BLA, abolishes the effects of GCs on memory (2,10). The impact

of stress on learning is further modulated by the emotionality of the 'to be learned' material (8,9) and is additionally influenced by the context in which learning takes place.

GCs exert their action in the central nervous system via the MR and the GR. Classically, GCs were considered to act exclusively at intracellular receptors involving rather slow genomic actions. However, more recently, evidence for rapid effects of GCs via membrane-bound versions of the MR (11) and GR (see below) has accumulated. The effects of GCs on memory have been mostly ascribed to the GR, whereas the effects of the high-affinity MR have been primarily associated with stress appraisal and responsiveness to stressful stimuli (11).

The current brief and selective review provides an overview of recent developments in several areas. It builds upon a symposium held at the 45th meeting of the International Society for Psychoneuroendocrinology entitled 'How Stress Influences Emotional Memories: A Translational Approach'.

First, the role of the endocannabinoid system in mediating the rapid, nongenomic effects of GCs on memory is illustrated in rodents. Subsequently, studies on the impact of a selective stimulation of the MR on different memory processes are reviewed. Next, a series of human experiments on the impact of stress or GC treatment on extinction and reconsolidation of fearful memories is presented. Finally, the clinical relevance of these findings is highlighted by the description of several patient studies.

Endocannabinoid mediation of the effects of GCs on memory

Classically, GCs were assumed to regulate physiology and behaviour through genomic pathways that involve the activation of intracellular GRs and subsequent changes in gene transcription (12). However, accumulating evidence indicates that some effects of GCs occur in a rapid fashion that is not compatible with the time frame of genomic actions. Thus, these more rapid effects appear to involve a nongenomic mechanism mediated by membrane-associated GC receptors (12,13). Previous studies have indicated that emotional arousal induces noradrenergic activation within the BLA and that GCs rapidly facilitate this noradrenergic activation to induce memory enhancement, yet the possible mechanism underlying this fast interaction is not well understood (2,14,15). Recently, the endocannabinoid system, a fast-acting retrograde messenger system, has emerged as a candidate for regulating the nongenomic actions of GCs in the brain (16–18). Endocannabinoids such as anandamide and 2-arachidonoyl glycerol (2-AG) are synthesised on demand and serve as retrograde messengers at central synapses (19). Through the activation of cannabinoid type 1 (CB1) receptors at presynaptic sites, they inhibit ion channel activity and reduce neurotransmitter release in the brain (20). In a series of experiments conducted in rats, Atsak *et al.* (21) examined the role of endocannabinoid signalling within the BLA in mediating the effects of GCs on noradrenergic function and the consolidation of memory.

In the first experiment, it was found that a selective GR agonist or membrane-impermeable GC ligand administered into the BLA immediately after inhibitory avoidance training enhanced long-term memory of the training. Strikingly, blockade of CB1 receptors in the BLA prevented the GC-induced memory enhancement. Furthermore, as expected, systemic post-training injections of a memory-enhancing dose of corticosterone increased neuronal activity within the BLA, as assessed by the number of cells expressing phosphorylated cAMP response-element binding (pCREB) protein shortly after the inhibitory avoidance training. However, a CB1 receptor antagonist administered systemically together with the corticosterone blocked the increased pCREB expression in the BLA. These findings demonstrate that endocannabinoid signalling in the BLA is essential for mediating the effects of GCs on the enhancement of memory and BLA activity.

Next, studies investigated whether activation of endocannabinoid signalling in the BLA is sufficient to enhance memory consolidation *per se* and whether this cannabinoid effect requires concurrent noradrenergic activation in the BLA. An activation of CB1 receptors with the cannabinoid agonist in the BLA induced a dose-dependent enhancement of inhibitory avoidance memory; however, co-infusion of the β-adrenoceptor antagonist propranolol prevented this memory enhancement. Such an enhancement of memory consolidation by cannabinoid activation is consistent with the findings of other studies and also occurs in other brain regions (22). These findings thus indicate that noradrenergic signalling is required for endocannabinoids to induce memory consolidation enhancement.

Further studies investigated whether endocannabinoids regulate the memory-modulatory effects of GCs via nongenomic influences on the noradrenergic system within the BLA. A suppression of GR signalling by administering a specific GR antagonist is known to reduce the sensitivity of the BLA to the memory-enhancing effects of noradrenergic stimulation, such that a much higher dose of the β-adrenoceptor agonist is required to induce memory enhancement (23). It was assumed that, if the endocannabinoid system is the primary route through which GCs change the sensitivity of the BLA to noradrenergic activation, then pharmacological augmentation of cannabinoid activity with an ineffective dose of the CB1 receptor agonist should compensate for the dose-shift induced by the blockade of GRs. Indeed, although the low dose of the CB1 receptor agonist *per se* was not sufficient to enhance memory, it completely blocked the effect of the GR antagonist with respect to reducing the sensitivity of the BLA to clenbuterol. These findings demonstrate that an enhancement of cannabinoid signalling totally compensates for the lack of GR activation and normalises the sensitivity of the BLA to noradrenergic stimulation. These findings also suggest that endocannabinoid signalling is the primary pathway through which GCs enhance memory consolidation and increase the sensitivity of BLA neurones to the memory-enhancing effects of noradrenergic activity. This interpretation is in accordance with the literature indicating that GCs, possibly through binding to a membrane-associated receptor, rapidly induce anandamide release in the amygdala (18,24). Moreover, the heightened anandamide signalling in the BLA after inhibitory avoidance learning is required for the optimal enhancement of memory consolidation (25). Taken together, and as illustrated in Fig. 1, our working model (21) suggests that GCs, via activation

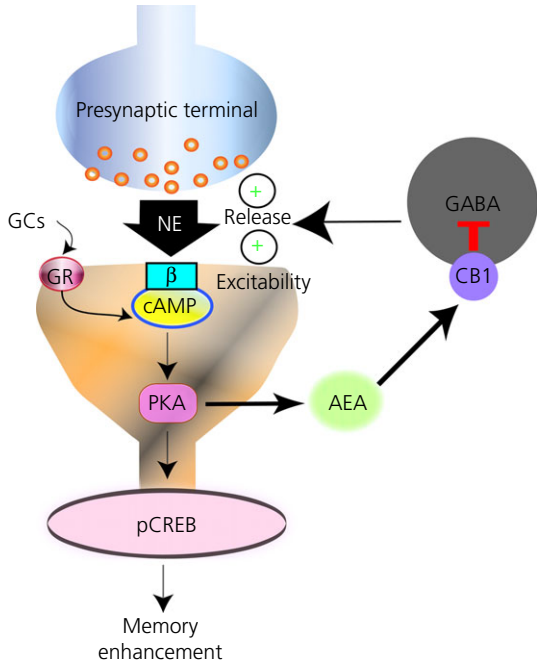

Fig. 1. The model illustrates the role of the endocannabinoid system in integrating the effects of glucocorticoids (GCs) and norepinephrine (NE) on memory consolidation. GCs, released during emotionally arousing situations, bind to a membrane-bound glucocorticoid receptor (GR), and activate the intracellular cAMP/protein kinase A (PKA) signalling cascade. This triggers endocannabinoid, particularly anandamide (AEA), synthesis. Endocannabinoids then activate cannabinoid type 1 (CB1) receptors on GABAergic terminals and thereby inhibit GABA release. This subsequently disinhibits NE release, and increases the excitability of pyramidal neurones within the basolateral complex of the amygdala (BLA). This overall increases the sensitivity of BLA neurones to NE. Together, these effects result in an increased activation of the cAMP/PKA pathway and phosphorylation of cAMP response-element binding (CREB) protein. These stress hormone effects in the BLA are required for the optimal enhancement of memory for emotionally arousing experiences. A similar working model might hold true for the hippocampus but likely involves a different endocannabinoid ligand Adapted from citation (21).

of a membrane-bound GR and intracellular pathways, induce the release of endocannabinoids, possibly anandamide (21). Because CB1 receptors within the BLA are predominantly found on local inhibitory GABAergic interneurones (26), GC-induced anandamide signalling might subsequently suppress GABAergic activity (27) and thereby disinhibit norepinephrine release and at the same time increase the excitability of BLA pyramidal neurones. Importantly, similar interactions between GCs and the endocannabinoid system have been reported in other brain regions (e.g. the hippocampus) to modulate fear memory consolidation (28) or other types of memory processes such as memory retrieval. However, in the latter case, 2-AG appears to have a more prominent role than anandamide (29,30). These findings have important implications for our understanding of the essential role of the endocannabinoid system in mediating rapid interactions between GCs and the noradrenergic arousal system.

The impact of MR stimulation on human cognition

Most of the effects of GCs on cognition have been attributed to GR function but, within the last two decades, more studies have emphasised the importance of the MR. In healthy individuals, blocking the MR typically leads to impaired cognitive performance (31–33). In addition, evidence from animal studies suggests that enhancing MR function improves memory performance (34). Based on this research, we aimed to investigate the effects of MR stimulation on cognition in humans. For this purpose, in a series of placebo-controlled studies, the effects of fludrocortisone, an MR agonist, on cognition in healthy individuals, patients with major depressive disorder (MDD) and patients with borderline personality disorder (BPD) were investigated (35–37). Of note, alterations of the HPA axis have been reported for MDD and BPD, including enhanced cortisol release and a reduced feedback sensitivity of the axis (38). The latter has been mostly interpreted in terms of disturbed GR functioning. In MDD, several studies have investigated GR function directly, whereas less research has been carried out in BPD patients. There is evidence for diminished GR function in MDD; for example, increased DNA methylation of the GR gene promoter (39) and reduced GR mRNA levels (40). There are also studies suggesting that MR dysfunction might play a role in the context of depression. For example, the inhibitory effect of fludrocortisone on cortisol secretion appears to be attenuated in patients with MDD, especially in individuals with psychotic symptoms (41). In addition, a reduced MR expression in the hippocampus and prefrontal cortex of MDD patients has been reported (42,43). Interestingly, there is evidence that cognitive deficits in psychiatric disorders, especially in MDD, are associated with alterations of the HPA axis (44). For example, studies have observed correlations between cortisol hypersecretion and impaired cognition in MDD (45,46).

In the first study, healthy individuals randomly received 0.4 mg of fludrocortisone or placebo orally in a double-blind, cross-over study design, which took place in the afternoon (35). Fludrocortisone improved performance in a wide range of neuropsychological tests, including visuospatial memory, working memory and verbal memory. These findings are in line with the hypotheses that MR activity (along with a moderate GR occupation) might facilitate hippocampal and prefrontal function, and thus enhance cognitive performance (47,48).

In a second step, studies investigated whether the enhancing effects of MR stimulation are also seen in psychiatric patients suffering from MDD and BPD. Again, the above-mentioned placebo-controlled, cross-over design was used in which fludrocortisone or placebo was administered in medication-free depressed patients and age-, sex- and education-matched healthy participants. In accordance with the literature, patients with MDD had worse cognitive performance compared to healthy individuals. Interestingly, across groups, test performance was improved for verbal memory and executive function after fludrocortisone compared to placebo (36), indicating that both groups appear to profit from MR stimulation.

In a BPD sample, a different pattern of the effects of MR stimulation on cognition was seen. That study compared medication-free

female BPD patients with healthy control women. BPD patients showed an impaired test performance after fludrocortisone treatment compared to placebo but only on hippocampus-mediated verbal memory and visuospatial memory. Working memory, which depends more on the prefrontal cortex, was improved after MR stimulation comparable to healthy controls (37). Thus, it appears that the effects of MR stimulation in BPD differ, depending on the brain region that is primary being examined with the used tasks. Possibly, MR function is intact in prefrontal brain areas in concert with disturbed MR function in limbic areas.

In sum, the reviewed studies have observed (in line with studies in rodents) that MR stimulation has beneficial effects on cognition. This was seen for both healthy individuals and depressed patients. In borderline patients, the findings appear to be more complex and the effects of MR stimulation appear to be task specific. Future studies should systematically disentangle the beneficial and adverse effects of MR stimulation in health and disease. In the studies reviewed here, fludrocortisone was given orally approximately 90 min before testing. Therefore, it is possible that not only the fast nongenomic effects of MR stimulation were seen, but also the slow genomic effects had already kicked in (49). Thus, in future human studies, it would be important to differentiate genomic from nongenomic MR effects.

How stress influences fear extinction and fear reconsolidation

So far, this review has focused on the impact of GCs in enhancing memories. However, humans and other animals not only have to acquire new information, but also have to update or unlearn old information and its associated behaviour when it is no longer relevant or appropriate. This is especially relevant for the treatment of anxiety disorders where patients have to transform an acquired association (e.g. a spider is dangerous) into a new safe association (e.g. a spider is not dangerous). This part of the review describes human experimental studies testing the impact of stress or GC treatment on extinction and reconsolidation of fearful memories. It thus paves the way for the clinical studies described in the final section of this review.

Classical fear conditioning is a powerful model for studying the development and treatment of anxiety disorders. The fear memory trace created initially 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- and state-dependent, as illustrated by several recovery phenomena (e.g. renewal, reinstatement, spontaneous recovery) (50). Stress, via its impact on the amygdala, the hippocampus and the prefrontal cortex, can influence memory extinction and its retrieval (51).

In the case of extinction learning and extinction retrieval, the highly relevant question arises as to whether stress influences the original acquisition memory trace or the later developed inhibitory extinction memory trace (51). Studies in anxiety patients reported that cortisol enhances the success of exposure-based therapies (see below) (52). By contrast, clinical observations suggest that stress is linked to the return of fear in anxiety patients, indicative of a negative impact of stress on extinction retrieval (53).

A series of human studies tested the impact of acute stress on extinction retrieval by using a renewal paradigm (54,55). In this paradigm, participants learn an association in context A. Afterwards, extinction takes place in another context (B). One day later, extinction retrieval is tested in both contexts. Typically, the conditioned response returns more strongly in the initial acquisition context, a phenomenon termed ABA renewal (56). Two different paradigms were used: a rather neutral and cognitive predictive learning task (54) and an emotional fear consolidation task (55). Stress was induced using the socially evaluated cold pressor task. The results revealed that stress impaired extinction retrieval in the predictive learning task but impaired the retrieval of the original fear memory trace in the fear-conditioning task. The two studies illustrate that the effect of acute stress on the retrieval of extinction memory depends among other things on the emotionality of the two memory traces. The findings are in line with the hypothesis that the more emotional the memory trace, the more pronounced is the effect of stress exposure on this trace (57). In patients with anxiety disorders, the situation might be different because their original acquisition memory trace is typically substantially older than the extinction trace and might thus be less influenced by stress (58). Moreover, the conditioned response often has become habitual and thus also less sensitive to stress (59).

In a next step, the impact of stress on extinction consolidation was investigated. Again, the two different learning paradigms were used. The results revealed that post-extinction stress led to a more context-dependent extinction memory, which was associated with a more pronounced renewal effect (60,61). These findings are in line with rodent studies indicating a critical role for GCs for contextual fear conditioning (62,63). They suggest that acute stress directly after extinction learning should be avoided to prevent an enhanced context dependency of this memory trace. By contrast, pre-extinction stress made extinction less context-dependent. The latter findings fit well with the clinical studies discussed later (52).

In sum, these experimental studies in humans illustrate that stress influences extinction and its retrieval. The effects are phase-dependent and are further modulated by the emotionality of the learning material. The findings not only highlight the potential, but also the risk associated with the occurrence of a stress-induced HPA response within the context of extinction-based treatment approaches.

Interference with reconsolidation has been proposed as an attractive alternative to extinction-based therapies. The use of beta blockers has been successful in abolishing fear-related memories in laboratory studies with healthy participants (64). Moreover, initial evidence suggests that this approach could be effective in the treatment of patients with specific phobias (65). With respect to fear conditioning, cortisol given during reactivation of a fear memory trace leads to a substantial and specific strengthening of the reconsolidated memory trace. This became apparent during reinstatement testing 24 h after reconsolidation manipulation (66). This finding might help to explain the persistence of fear memories in psychopathology. Moreover, the enhancing effect of cortisol on fear

memory reconsolidation suggests that GCs should not be used during reconsolidation-based therapeutic interventions.

GCs as a treatment or as an adjuvant treatment for anxiety disorders

GCs enhance the consolidation of new memories (67); on the other hand, these hormones can reduce the retrieval of information that has already been stored (8). Moreover, as described above, there is evidence available to indicate that emotionally arousing information is especially sensitive to the memory-modulating effects of stress and GCs (8).

Enhanced consolidation of emotionally arousing information is an adaptive mechanism that helps us to retain important information. Reduced memory retrieval may help to reduce behaviours that are no more relevant or even maladaptive. This mechanism might become important in chronic situations when there is a need for adaptation to a changed environment (e.g. environmental disaster or war) (8). Under such conditions, the facilitating effects of GCs on extinction may also support adaptation (68,69).

Because emotionally aversive memories play a crucial role in the development and symptomatology of anxiety disorders, we aimed to translate the basic findings to clinical conditions. Specifically, the results obtained, which indicated that GCs reduce memory retrieval and enhance the extinction of emotional memories, proposed that these stress hormones might be helpful in the treatment of anxiety disorders.

Clinical studies in patients with post-traumatic stress disorder and phobias (70–72), as well as studies in animal models of acquired fear (73), indicate that GC treatment indeed reduces the retrieval of aversive memories and enhances extinction processes. These dual actions of GCs appear to be especially suited for the treatment of acquired fear. By inhibiting memory retrieval, GCs may reduce symptoms related to aversive memories. Furthermore, by enhancing the consolidation of extinction memory, GCs might facilitate the storage of experiences associated with less fear. An illustration of this model is provided in Fig. 2. Therefore, adding GCs to exposure techniques in extinction-based psychotherapy may be a promising approach. Indeed, initial evidence indicates that combining cortisol with exposure therapy increases treatment success in patients with a fear of heights (52). Similar findings were obtained in patients with spider phobia (74).

Recently, novel evidence was provided showing that GC administration can reduce craving in heroin addicts (75). There is growing evidence that memory and addiction partly share neural circuitries and molecular mechanisms (76). Importantly, the powerful incentives associated with drug taking that produce a strong feeling of craving are stored in memory; also referred to as addiction memory (77). Thus, GCs may have reduced craving by interfering with the retrieval of addiction memory (75).

Finally, recent evidence indicates that the effects of stress and GCs on memory are influenced by genetic variation of the GR (78,79) and by epigenetic modification of the GR gene promoter (80,81). These findings may add to the understanding of why some individuals are more sensitive to the effects of stress than others.

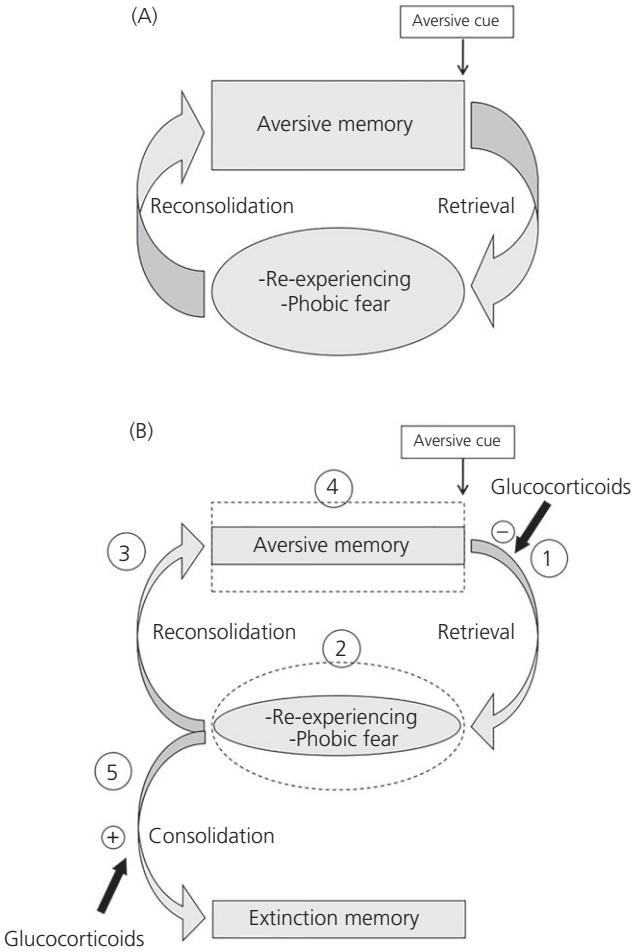

Fig. 2. Model on the role of glucocorticoids in the reduction of aversive memory. (A) Excessive retrieval of aversive memories causes re-experiencing symptoms in post-traumatic stress disorder and phobic fear in phobia. Reconsolidation of such aversive experiences further cements the aversive memory trace. (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. Reproduced with permission (8).

Future research should include large-scale clinical studies evaluating the therapeutic efficacy of GCs in the treatment of anxiety disorders and addiction and exploring the efficacy of combining GC treatment with psychotherapy.

Summary and outlook

The present review illustrates that the impact of stress on memory consolidation is mediated by a rapid activation of endocannabinoid signalling by GCs during emotionally arousing conditions. Such

findings might carry important implications for maladaptive stress responses. Changes in GC (82), endocannabinoid (83–85) and catecholaminergic (86) signalling have been repeatedly reported in individuals after malignant stress exposure, as well as in those at risk of post-traumatic stress disorder. Thus, these recent findings might help to enhance our understanding underlying maladaptive stress responses and also open up new venues for pharmacological intervention targeting the endocannabinoid system.

Mounting evidence is accumulating showing that stimulation of the MR is beneficial to a range of cognitive and affective tasks. It remains to be shown which particular cognitive process is mediating the rather broad beneficial effects observed. Moreover, the possibility of a differential impact on specific memory phases and/or an interaction with the emotionality of the learning material needs to be examined (7,9). The role of intracellular versus membrane-bound MRs in mediating these effects is currently incompletely understood (11). Moreover, the interaction with the GR and the possible cross-talk with the endocannabinoid system described above remain as future research challenges.

Stress influences extinction and extinction retrieval (51). These effects are learning-phase dependent and are further modulated by emotional arousal and context. In addition, cortisol enhances the reconsolidation of fear memory (66). These findings highlight not only the potentially beneficial, but also the potentially detrimental effects of GCs within the context of treatment approaches for anxiety disorders (87).

Finally, work by de Quervain and coworkers has illustrated that GCs can reduce anxiety and boost extinction-based therapeutic interventions in patients with anxiety disorders. These effects might also be helpful for the treatment of addictions. Last but not least, it has become evident that the impact of stress and stress hormones on memory is modulated by genetic and epigenetic processes (80,88).

Taken together, in recent years, substantial progress not only in our mechanistic understanding, but also in the clinical potential of the memory-modulating properties of stress hormones has been made. At the same time findings, obtained in the four areas discussed in the present review emphasise the need for future studies addressing the unresolved issues discussed above.

Received 11 November 2015,
revised 14 December 2015,
accepted 16 December 2015

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