Chapter 5
Role of Endocannabinoids in Regulating Glucocorticoid Effects on Memory for Emotionally Arousing Experiences

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Abstract There is extensive evidence that glucocorticoid hormones, normally released from the adrenal cortex during stressful events, enhance the consolidation of long-term memory of emotionally arousing training experiences, yet impair the retrieval of previously acquired information during emotionally arousing test situations. In contrast, glucocorticoids have little effect on the consolidation or retrieval of memory of low-arousing or neutral information. Although it is now well established that glucocorticoid effects on these two memory functions depend on rapid interactions with arousal-induced noradrenergic activity within the basolateral amygdala and several other brain regions, the exact neurobiological mechanism underlying this presumably nongenomically mediated glucocorticoid action remained to be elucidated. In this chapter, we present compelling evidence indicating that the endocannabinoid system, a rapid lipid signaling system in the brain, plays an essential role in regulating glucocorticoid effects on different memory processes via actions through a membrane-associated glucocorticoid receptor.

Abbreviations

AEA	Anandamide
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
BLA	Basolateral complex of the amygdala
CB1	Cannabinoid receptor type 1
CB2	Cannabinoid receptor type 2
cort-BSA	Corticosterone conjugated to a bovine serum albumin molecule
CREB	cAMP response-element binding protein

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pCREB	Phosphorylated CREB
HDAC	Histone deacetylase
HPA-axis	Hypothalamus-pituitary-adrenocortical-axis
GABA	Gamma Amino Butyric Acid
GR	Glucocorticoid receptor
PKA	cAMP-dependent protein kinase
PTSD	Posttraumatic stress disorder
THC	Tetrahydrocannabinol
2-AG	2-arachidonoylglycerol

5.1 Introduction

Stress is defined as any stimulus that represents a perceived or actual threat to the psychological and physiological equilibrium of an organism (Selye 1976). As a response to stress, the organism strives to reinstate homeostasis by activating several autonomic and humoral stress-response systems. Typically, stress leads to an activation of the sympathetic nervous system and HPA-axis, culminating in the release of catecholamines and glucocorticoids from the adrenal medulla and cortex, respectively (McCarty and Gold 1981; de Boer et al. 1990; Roozendaal et al. 1996b). These hormones promote the organism's ability to cope with stress by acting on target systems in the periphery but also inducing a myriad of effects on the brain. In addition to preparing an individual for the acute consequences of dangerous or threatening situations and the return to homeostasis, an important function of the stress response is to induce long-term adaptive changes (McEwen 1998, 2001). For instance, stressful or emotionally arousing life events typically leave lasting and vivid memories. Extensive evidence indicates that glucocorticoid hormones, in concert with several other stress-activated systems, mediate the selective better storage of memory of emotionally significant experiences (Oitzl and de Kloet 1992; Sandi and Rose 1994; de Kloet et al. 1999; Roozendaal 2000; Joëls and Baram 2009; Roozendaal et al. 2009a). While this is considered to be a highly adaptive survival mechanism that enables the organism to retain lasting memories of biologically significant life events, intense emotional experiences such as automobile accidents, fires, muggings, rapes, wartime battles, or terrorists' bombings can also create maladaptive traumatic memories and result in the development of psychiatric disorders such as (PTSD).

It is now well established that stress and glucocorticoid hormones do not only influence the formation and long-term storage of new memories, but also affect the remembrance of previously acquired information. In contrast to the enhancing effects of glucocorticoids on memory consolidation, these hormones typically impair the retrieval of memory processing (de Quervain et al. 1998; Het et al. 2005). However, glucocorticoids do not modulate memory of all experiences alike; rather, they appear to preferentially influence the consolidation and retrieval of memory of emotionally arousing experiences. Extensive evidence from our as well as other

laboratories indicates that this selectivity derives from a critical dependence of glucocorticoid actions on concomitant arousal-induced activation of noradrenergic transmission within the (BLA) as well as several other brain regions (Roozendaal et al. 2006a, 2009a). Despite the different time courses of these hormones, i.e., norepinephrine is rapidly released within the brain followed several minutes later by a rise of glucocorticoid levels in general circulation, there appears to be an overlapping presence of norepinephrine and glucocorticoids in time and space that allows the stage for interactions (Joëls et al. 2011). Importantly, recent evidence indicates that such interplay between glucocorticoids and the noradrenergic system is not mediated via the classical genomic action of glucocorticoids but likely to involve fast actions through an activation of membrane-associated steroid receptors.

The scope of this chapter is to summarize recent findings on some novel mechanisms underlying the acute effects of glucocorticoid hormones on memory. We will first summarize the opposing effects of glucocorticoids on memory consolidation and memory retrieval. Then, we will describe how glucocorticoids interact with noradrenergic activity within the BLA to selectively modulate memory of emotionally arousing experiences. Finally, we will present evidence indicating a critical involvement of the endocannabinoid system, a fast-acting lipid system in the brain, in mediating such rapid effects of glucocorticoids onto the noradrenergic system in influencing both the consolidation and retrieval of memory of emotionally significant experiences.

5.2 Acute Glucocorticoid Effects on Memory Consolidation and Retrieval

Over the last decades, considerable evidence has accumulated indicating that glucocorticoids (cortisol in humans, corticosterone in rodents) are crucially involved in modulating memory processes. Early reports on both enhancing and impairing properties of glucocorticoids on memory have revealed that these hormones have complex effects on cognitive functions (Bohus and Lissak 1968; Flood et al. 1978; Beckwith et al. 1986; Luine et al. 1993; Arbel et al. 1994). However, more recent studies investigating glucocorticoid effects on distinct memory phases allowed for a disentangling of the multifaceted actions of these stress hormones. Glucocorticoids are now known to enhance the consolidation of memory of emotionally arousing experiences, but to impair memory retrieval and working memory during emotionally arousing test situations (de Quervain et al. 1998; Roozendaal 2000; Roozendaal et al. 2004b; de Quervain et al. 2009).

There is extensive evidence from animal studies that glucocorticoids are critically involved in regulating the consolidation of memory processing (Flood et al. 1978; de Kloet 2000; Roozendaal 2000; McGaugh and Roozendaal 2002). Acute administration of corticosterone or a specific GR agonist typically enhances long-term memory consolidation when given either before or shortly after a training

experience (Flood et al. 1978; Sandi and Rose 1994; Pugh et al. 1997; Roozendaal et al. 1999a; Cordero et al. 2002). In contrast, a blockade of glucocorticoid production with the synthesis inhibitor metyrapone impairs memory consolidation (Roozendaal et al. 1996a; Maheu et al. 2004) and prevents stress-induced memory enhancement (Roozendaal et al. 1996b; Liu et al. 1999). 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 (Roozendaal et al. 1999b). 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 (Roozendaal et al. 2006a). 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 consolidation have mostly been investigated with respect to declarative memory(Het et al. 2005; Wolf 2008).

Recent findings indicate that glucocorticoids enhance memory consolidation of emotionally arousing training experiences but do not affect the consolidation of emotionally 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 (Okuda et al. 2004). Although no rewarding or aversive stimulation is used during this learning paradigm, training on this task induces modest novelty-induced stress or arousal (de Boer et al. 1990). However, extensive habituation of rats to the experimental context (in the absence of any objects) reduces the arousal component of the task during the training. We found that corticosterone, administered systemically immediately after training, enhanced 24-h retention of rats that were not previously habituated to the experimental context. In contrast, posttraining corticosterone administration 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 (Okuda et al. 2004). Human studies support the hypothesis that learning-associated arousal is a prerequisite for the enhancing effects of glucocorticoids on memory consolidation (Abercrombie et al. 2006; Wolf 2008; de Quervain et al. 2009; van Stegeren et al. 2010).

In contrast to the enhancing effects of glucocorticoids on memory consolidation, these hormones typically impair memory retrieval. In the first study investigating the effects of stress and glucocorticoids on retrieval processes, de Quervain et al. (1998) reported that 30 min after exposure to footshock stress, rats had impaired retrieval of spatial memory on 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 stress exposure. These time-dependent effects of stress exposure on retrieval processes corresponded to the circulating corticosterone levels at the time of retention testing, which suggested that the retrieval impairment might

be directly related to stress-induced increases in adrenocortical function. In support of this idea, we found that suppression of corticosterone synthesis with metyrapone blocked the stress-induced impairment in memory retrieval. Moreover, systemic corticosterone administered to nonstressed rats 30 min before retention testing induced dose-dependent retrieval impairment (de Quervain et al. 1998). In the next step, we translated these findings to healthy humans and found that a single administration of cortisone shortly before retention testing impaired free recall of words learned 24 h earlier (de Quervain et al. 2000). Several further studies from different laboratories have indicated that stress exposure, glucocorticoids or selective GR agonists (such as dexamethasone and RU 28362) impair the retrieval of hippocampus-dependent spatial or contextual memory in rats and declarative (mostly episodic) memory in humans (Wolf et al. 2001; Roozendaal et al. 2003; Buss et al. 2004; Rashidy-Pour et al. 2004; Roozendaal et al. 2004b; Het et al. 2005; Kuhlmann et al. 2005a; Sajadi et al. 2007; Coluccia et al. 2008; Wolf 2008), yet few studies revealed that the impairing effects of stress and glucocorticoids extend to hippocampus-independent memory tasks (Guenzel et al. 2013). Highly comparable to the previously described effects of glucocorticoids on memory consolidation, these hormones selectively impair the retrieval of memory of emotionally arousing information or during emotionally arousing test situations (Kuhlmann et al. 2005a; Kuhlmann et al. 2005b; de Quervain et al. 2007; Smeets et al. 2008).

5.3 Glucocorticoids Interact with Noradrenergic Mechanisms Within the Basolateral Amygdala

As summarized up to this point, glucocorticoids selectively modulate the consolidation and retrieval of memory of emotionally arousing, but not of emotionally neutral, information. An apparent question is what neurobiological mechanism might underlie this selectivity? Our findings indicate that interactions between glucocorticoids and arousal-induced noradrenergic activity within the BLA may be key in determining this selectivity. It is well established that emotionally arousing training experiences that induce the release of adrenal stress hormones also increase BLA neuronal activity (Pelletier et al. 2005). Norepinephrine is also released into the amygdala during emotionally arousing training (Galvez et al. 1996; Quirarte et al. 1998; McIntyre et al. 2002), whereas posttraining infusion of norepinephrine or a β-adrenoceptor agonist into the BLA enhances memory of training on several learning tasks (Ferry and McGaugh 1999; Hatfield et al. 1999; LaLumiere et al. 2003; Roozendaal et al. 2008). Considerable evidence indicates that glucocorticoids interact with this training-associated noradrenergic activation within the amygdala in enhancing the consolidation of memory of emotionally arousing training experiences (Roozendaal et al. 2009a). For example, as shown in Fig. 5.1, an in vivo microdialysis study reported that the administration of a memory-enhancing dose of corticosterone after inhibitory avoidance training rapidly augmented norepinephrine levels within the amygdala (McReynolds et al. 2010). In contrast,

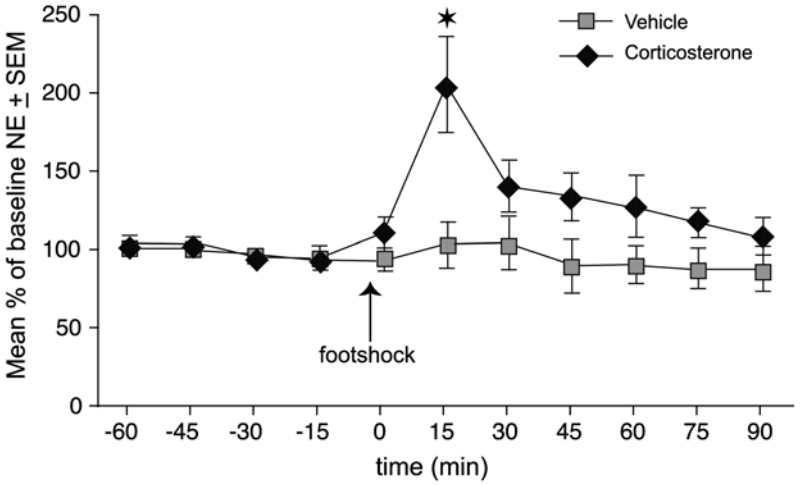

Fig. 5.1 Effect of immediate posttraining corticosterone treatment on norepinephrine (NE) levels in the basolateral complex of the amygdala (BLA). Microdialysis samples were collected every 15 min. Norepinephrine levels (mean ± SEM) are expressed as a percentage change from average baseline levels. Corticosterone treatment (3 mg/kg, i.p.) significantly increased norepinephrine release in the amygdala of animals trained on an inhibitory avoidance task compared with vehicle-injected animals. $*p < 0.05$ versus vehicle. (Adapted from McReynolds et al. 2010, with permission)

the same dose of corticosterone, administered to nontrained control rats did not modify amygdala norepinephrine levels. Moreover, attenuation of noradrenergic signaling with the β-adrenoceptor antagonists propranolol or atenolol infused into the BLA, but not into the neighboring central amygdala, blocked the memory enhancement induced by a glucocorticoid administered either systemically or directly into the BLA (Quirarte et al. 1997; Roozendaal et al. 2002). In subsequent studies we showed that glucocorticoids enhance memory consolidation, in a permissive fashion, by potentiating β-adrenoceptor-PKA efficacy and downstream phosphorylation of CREB protein (Roozendaal 2002; Roozendaal et al. 2002; Roozendaal et al. 2006a; Roozendaal et al. 2010). Importantly, a β-adrenoceptor antagonist infused into the BLA also prevented memory consolidation enhancement induced by a glucocorticoid administered into other brain regions, including the hippocampus (Roozendaal et al. 1999a), supporting the general hypothesis that norepinephrine-induced BLA activity is required for regulating neural plasticity and information storage processes in its many efferent brain regions (McGaugh 2004).

Based on the evidence summarized above, it may be hypothesized that an arousal-induced increase in noradrenergic activity within the BLA is essential in enabling glucocorticoid effects on memory consolidation. Such a mechanism may then provide a direct explanation for the finding that glucocorticoids selectively enhance memory consolidation of emotionally arousing experiences. We investigated this issue in rats trained on an object recognition task. As already mentioned, corticosterone enhances memory of object recognition training when administered to

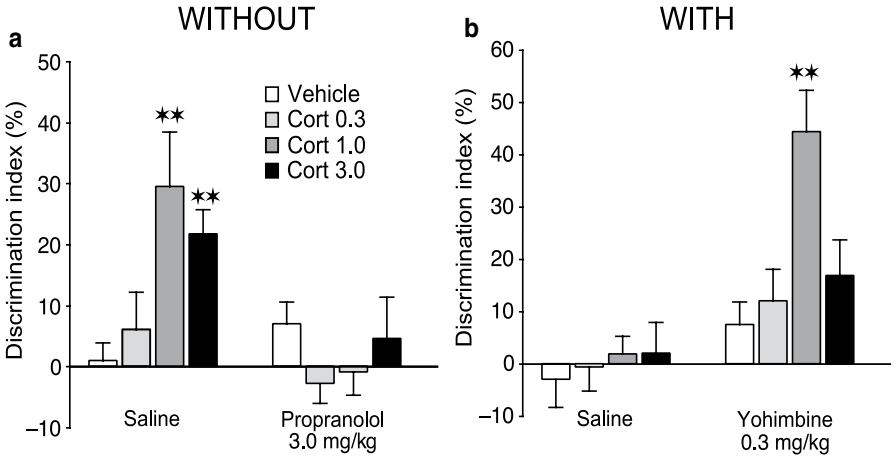

Fig. 5.2 Glucocorticoid effects on memory consolidation for object recognition training require arousal-induced noradrenergic activation. Rats were either habituated to the training context for 7 days (*WITH*) or not habituated (*WITHOUT*). On day 8, they were given a 3-min training trial during which they could freely explore two identical objects, training was followed by systemic drug administration. Retention was tested 24 h later by placing the rats back into the apparatus for 3 min; in this trial, one object was similar to the training objects whereas the other was novel. Data represent discrimination index (%) on a 24-h retention trial, expressed as mean ± SEM. The discrimination index was calculated as the difference in the time spent exploring the novel and the familiar object, expressed as the ratio of the total time spent exploring both objects. **a** Effects of immediate posttraining administration of the β-adrenoceptor antagonist propranolol (3 mg/kg, s.c.) on corticosterone (0.3, 1.0, 3.0 mg/kg, s.c)-induced enhancement of object recognition memory in naïve (emotionally aroused) rats. **b** Effect of co-administration of the α_2-adrenoceptor antagonist yohimbine (0.3 mg/kg, s.c.) with corticosterone on object recognition memory in habituated (emotionally nonaroused) rats. $^{**}p < 0.0001$ versus vehicle. (Adapted from Roozendaal et al. 2006b)

naïve rats, but is ineffective when training-associated arousal levels are reduced by extensive prior habituation (Okuda et al. 2004). In a follow-up study we found that, in nonhabituated (i.e., emotionally aroused) rats, the β-adrenoceptor antagonist propranolol administered systemically after training blocked the corticosterone-induced memory enhancement (Roozendaal et al. 2006b). 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 was due to insufficient training-induced noradrenergic activation, low doses of the α_2-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. As shown in Fig. 5.2, the critical finding of this latter experiment is that such an augmented noradrenergic tone was sufficient to mimic the effects of emotional arousal in that simultaneously administered corticosterone now enhanced memory consolidation (Roozendaal et al. 2006b). Further, in habituated rats, corticosterone increased the activity of BLA neurons, as assessed by pCREB 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. Interestingly, a recent functional magnetic resonance imaging study confirmed that in humans also the amygdala is an important locus of glucocorticoid–norepinephrine interactions in enhancing memory of emotionally salient information (Van Stegeren et al. 2007).

Recent findings have shown that the BLA is not the only brain region mediating glucocorticoid interactions with the noradrenergic system in regulating memory consolidation. For example, we found that a β-adrenoceptor antagonist administered into the nucleus accumbens shell prevented glucocorticoid-induced memory enhancement on both an appetitive and aversive version of taste learning (Wichmann et al. 2012). Posttraining infusion of the GR agonist RU 28362 into the medial prefrontal cortex also enhances memory consolidation of inhibitory avoidance training (Roozendaal et al. 2009b), and a β-adrenoceptor antagonist or PKA inhibitor co-infused into the medial prefrontal cortex prevented this memory enhancement (Barsegyan et al. 2010). Moreover, corticosterone administered systemically immediately after inhibitory avoidance training increased PKA activity in the medial prefrontal cortex within 30 min. These findings suggested that glucocorticoid effects on noradrenergic signaling might have an onset that is too fast to be mediated via transcriptional regulation in the nucleus and likely involve a rapid, nongenomic mode of action. In support of the view that these glucocorticoid effects might require a GR that is located in or near the cell membrane, we found that posttraining infusion of corticosterone conjugated to a bovine serum albumin molecule (i.e., cort:BSA), a ligand that selectively activates adrenal steroid receptors on the cell surface, into the insular cortex enhanced memory consolidation, and that this enhancing effect was blocked by co-administration of a GR, but not mineralocorticoid receptor, antagonist (Roozendaal et al. 2010). In an entirely new line of research, we found that glucocorticoid effects on norepinephrine signaling and downstream pCREB activation in the insular cortex might enhance memory consolidation via chromatin modification (Roozendaal et al. 2010). Systemic corticosterone increased histone acetylation, a form of chromatin modification, in the insular cortex as assessed 1 h after training on an object recognition task. Furthermore, infusion of the HDAC inhibitor sodium butyrate administered into the insular cortex enhanced memory consolidation of this training. Inducing a histone hyperacetylated state via HDAC inhibition appears to facilitate transcription by relaxing chromatin structure, resulting in enhanced synaptic plasticity, and long-term memory processes (Barrett and Wood 2008). However, the effect of the HDAC inhibitor on memory enhancement was completely abolished by blocking GR activity. Additionally, a PKA inhibitor also blocked the ability of HDAC inhibition to enhance memory in the insular cortex. Thus, these findings indicate that inducing a histone hyperacetylated state via HDAC inhibition is not sufficient to enhance long-term memory. It is still necessary to have upstream signaling via GR and PKA activity. Presumably, these signaling events are triggering steps necessary to activate transcription factors and co-activators such as CREB and CREB binding protein.

Glucocorticoid effects on memory retrieval are highly comparable to the effects on memory consolidation in that emotionally arousing information or an emotionally arousing test situation, both inducing the release of norepinephrine, is required for enabling glucocorticoid effects on memory retrieval (Smeets et al. 2008; Wolf 2008; de Quervain et al. 2009; Roozendaal et al. 2009a). Systemic administration of the β-adrenoceptor antagonist propranolol blocked the memory retrieval impairment of spatial/contextual information induced by a concurrent injection of corticosterone (Roozendaal et al. 2004a). 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 the retrieval of spatial and contextual memory in animals and declarative memory in humans (Squire 1992; Moser and Moser 1998; Cabeza and Nyberg 2000). 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 (Roozendaal et al. 2003) and that a β-adrenoceptor antagonist co-infused into the hippocampus prevented the retrieval-impairing effect of the GR agonist (Roozendaal et al. 2004b). As stimulation of β_1-adrenoceptors with systemic injections of the selective agonist xamoterol induces memory retrieval impairment comparable to that seen after corticosterone administration (Roozendaal et al. 2004b), the findings suggest that glucocorticoid effects on memory retrieval impairment involve a facilitation of noradrenergic mechanisms. Further studies in animals have indicated that the BLA interacts with the hippocampus in mediating glucocorticoid effects on memory retrieval of emotionally arousing information (Roozendaal et al. 2003, 2004b). We found that the administration of a β-adrenoceptor antagonist into the BLA blocks the impairing effect of a GR agonist infused into the hippocampus on retrieval of spatial memory (Roozendaal et al. 2004b). Findings of animal studies addressing the importance of interactions between the amygdala and the hippocampus during retrieval of emotionally arousing information are corroborated by human imaging studies indicating 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 (Dolcos et al. 2005; Smith and Vale 2006).

Collectively, these findings indicate that glucocorticoids interact with the noradrenergic system in strengthening the consolidation of long-term memory of emotionally significant events, while at the same time inducing temporary impairment of the recall of previously acquired information. Figure 5.3 summarizes these findings. Given that the onset of such glucocorticoid interactions with the noradrenergic system is rapid and likely involves binding to a membrane-associated receptor for corticosterone, it is highly plausible that these glucocorticoid effects are mediated through a nongenomic mode of action. Therefore, in the next section we will first briefly discuss some general mechanisms that have been described in the literature that might regulate such rapid, nongenomic effects of glucocorticoids on physiology and behavior, followed by a more extensive discussion of the possible involvement of the endocannabinoid system in mediating such rapid glucocorticoid effects.

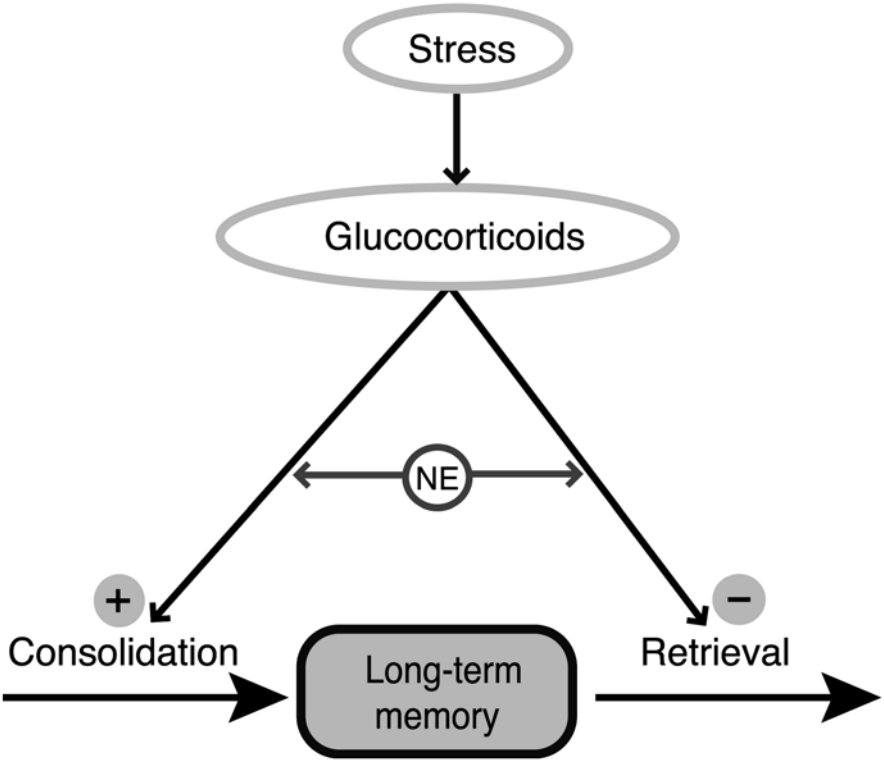

Fig. 5.3 Effects of stress and glucocorticoids on memory functions. Glucocorticoids enhance memory consolidation, whereas they impair memory retrieval. Both of these glucocorticoid effects depend on emotional arousal-induced noradrenergic activity. *NE* norepinephrine. (Adapted from de Quervain et al. 2009, with permission)

5.4 Nongenomic Glucocorticoid Actions

Glucocorticoids are known to modulate cellular function, including learning and memory, through both genomic (slow) and nongenomic (rapid) pathways (de Kloet 2000; Dallman 2005; Popoli et al. 2011). Genomic glucocorticoid effects are mediated by classical steroid mechanisms involving transcriptional regulation. Glucocorticoids can influence transcription through both DNA-binding–dependent and DNA-binding–independent mechanisms (de Kloet 2000). Although many glucocorticoid actions suit the time frame for a genomic mechanism, some behavioral and physiological effects of glucocorticoids, for example, the previously described effects on the noradrenergic system, have a rapid onset, occurring in seconds to minutes, that is not readily compatible with transcriptional regulation. Rapid glucocorticoid actions have been reported in different limbic and brainstem structures, where they control functions ranging from learning and memory to neuroendocrine functions (Dallman 2005; Tasker et al. 2006; Haller et al. 2008; Riedemann et al.

2010). It is important to note that glucocorticoid effects on the consolidation of long-term memory might depend on an interplay between genomic and nongenomic actions (Falkenstein et al. 2000), whereas glucocorticoids' ability to temporarily impair memory retrieval might depend solely on nongenomic glucocorticoid actions. In support of this view, it has been reported that protein synthesis inhibitors fail to prevent glucocorticoid effects on memory retrieval (Sajadi et al. 2006).

Nongenomic glucocorticoid actions likely involve the activation of a membrane-associated variant(s) of the steroid receptor (Losel et al. 2003; Dallman 2005; Tasker et al. 2006; Riedemann et al. 2010). Orchinik and colleagues (Orchinik et al. 1991; Rose et al. 1993) were the first to provide evidence that glucocorticoids exert behavioral effects through the activation of a corticosteroid receptor on the neuronal membrane. In this series of experiments, glucocorticoids rapidly suppressed mating behavior in the amphibian Taricha granulosa (rough-skinned newt) by binding to a receptor on neuronal membranes. As mentioned, recent findings indicate that the administration of the membrane-impermeable glucocorticoid ligand cort:BSA into a variety of brain regions of the rat is sufficient to enhance the consolidation of long-term memory of emotionally arousing training experiences (Roozendaal et al. 2010; Lee et al. 2011). As these cort:BSA effects are blocked by co-administration of a GR antagonist (Barsegyan et al. 2010; Roozendaal et al. 2010), these findings suggest a role for a membrane-associated GR in mediating rapid glucocorticoid effects on memory. Studies employing GR immunoreactivity, at both the light and the electron microscopic level, provided anatomical evidence for the existence of membrane-associated GRs in neurons of the hippocampus, hypothalamus (Liposits and Bohn 1993), and postsynaptic membranes of lateral amygdala neurons (Johnson et al. 2005).

Current evidence indicates a variety of nongenomic glucocorticoid actions on neuroplasticity and memory, ranging from a rapid increase in glutamate-release probability from presynaptic sites (Karst et al. 2005) to a rapid insertion of AMPA receptor subunits in postsynaptic membranes (Groc et al. 2008; Pasricha et al. 2011). Recently, the endocannabinoid system emerged as an important mediator of some of the rapid effects of glucocorticoids. The first evidence derived from in vitro studies indicating an involvement of endocannabinoids in mediating glucocorticoid-induced rapid inhibition of the HPA-axis within the hypothalamus (Di et al. 2003; Di et al. 2005a; Evanson et al. 2010; Hill and Tasker 2012). Consistently, later studies pointed out that both stress and glucocorticoids significantly alter endocannabinoid content in limbic brain regions that can function to both mount and terminate the stress response (Hill and McEwen 2010). Although the interest in endocannabinoid signaling as a candidate for mediating fast glucocorticoid effects has been quickly growing, it is noteworthy to also mention the existence of other candidate systems that might regulate rapid glucocorticoid actions. For instance, an activation of membrane GRs evokes the release of nitric oxide from pyramidal cells in the hippocampus (Hu et al. 2010) that acts as a retrograde messenger and induces the release of GABA from hippocampal interneurons and hypothalamic magnocellular neurons (Di et al. 2009; Hu et al. 2010). Glucocortiocoids also enhance glutamate transmission in hippocampal CA1 pyramidal neurons in the rat by a min-

eralocorticoid receptor-dependent mechanism. Although the mechanism underlying this fast mineralocorticoid receptor-mediated effect on glutamatergic transmission is not known, it has been shown not to rely on endocannabinoid signaling (Karst et al. 2005; Olijslagers et al. 2008).

5.5 Role of the Endocannabinoid System in Mediating Glucocorticoid Effects on Memory Consolidation and Retrieval

In the previous sections we have shown that glucocorticoids, because of critical interactions with arousal-activated noradrenergic mechanisms, selectively influence the consolidation and retrieval of emotionally arousing learning experiences or under emotionally arousing test situations. However, the onset of these glucocorticoid effects on the noradrenergic system is, at least in part, not readily compatible with its classical action of inducing transcriptional regulation in the nucleus. We have subsequently described several novel mechanisms by which glucocorticoids might be able to induce rapid and nongenomically mediated effects on physiology and behavior. In this section, we will first introduce the endocannabinoid system and give a brief overview of its general role in neuronal plasticity and learning and memory, and then we focus on recent findings indicating that the endocannabinoid system might be essentially involved in mediating the rapid effects of glucocorticoids onto the noradrenergic system in regulating both the consolidation and retrieval of memory.

5.5.1 The Endocannabinoid System in the Brain

The endocannabinoid system, a fast lipid system in the brain, recently emerged as an important stress-response system (Hill and Tasker 2012). It is composed of two G protein-coupled receptors, the CB1 and the CB2, and two endogenous cannabinoid ligands such as *N*-arachidonylethanolamine (AEA) and (2-AG). Endocannabinoids are produced upon activation by both neurons and glia cells and operate primarily as interneuronal signaling molecules (Freund et al. 2003; Kano et al. 2009). Cannabinoid receptors are also activated by external ligands such as plant-derived cannabinoids (e.g., THC, produced by the cannabis plant) and synthetic cannabinoids (e.g., WIN55,212-2). CB1 receptors are expressed almost ubiquitously throughout the brain (Katona et al. 1999, 2001), whereas CB2 receptors are mostly present in peripheral immunological tissues, but they have also been found within the central nervous system (Onaivi et al. 2006) Postsynaptic depolarization induces an elevation of intracellular Ca^{2+} concentrations that triggers the release of endocannabinoids into the synapse. Once released, endocannabinoids contribute to several forms of short-term and long-term synaptic plasticity by acting as a retrograde messenger and binding to CB1 receptors at the presynaptic membrane, eventually suppress-

ing neurotransmitter release either transiently or persistently (Hashimotodani et al. 2007; Kano et al. 2009). A vast number of studies demonstrated that CB1 receptor activation influences the release of various neurotransmitters, including glutamate, GABA, glycine, acetylcholine, norepinephrine, dopamine, serotonin, and cholecystokinin (Kano et al. 2009).

5.5.2 Cannabinoid Effects on Learning and Memory

The cannabinoid system emerged as an important modulator of different learning and memory processes (Wotjak 2005; Kano et al. 2009; Marsicano and Lafenetre 2009; Akirav 2011). Early studies, examining the effects of pretraining administration of cannabinoid agonists, in particular THC or WIN55212-2, reported impairing effects on the acquisition of water maze, contextual fear memory, and object recognition training in rodents (Lichtman et al. 1995; Da and Takahashi 2002; Pamplona and Takahashi 2006). Moreover, concurrent administration of the CB1 receptor antagonist/inverse agonist SR141716 (rimonabant) blocked these impairments (Lichtman et al. 1995; Da and Takahashi 2002; Pamplona and Takahashi 2006). More recent studies employing targeted pharmacological manipulations of the cannabinoid system by local infusions into the brain have illustrated more consistent results with regard to their wide-ranging effects on different memory phases. Pretraining administration of a CB1 receptor agonist into the hippocampus has consistently been shown to impair spatial learning (Lichtman et al. 1995; Egashira et al. 2002; Wegener et al. 2008; Abush and Akirav 2010). However, drug treatment given before a learning experience could affect performance by influencing nonspecific attentional, locomotor, and motivational processes during acquisition. To address whether cannabinoid drugs directly modulate the consolidation of memory, we investigated the effect of the CB receptor agonist WIN55,212-2 on long-term retention when infused into the BLA immediately after training on an inhibitory avoidance task. As shown in Fig. 5.4a and b, we found that WIN55,212-2 dose-dependently enhanced 48-h retention of this training, whereas the CB1 receptor antagonist AM251 administered posttraining into the BLA impaired memory consolidation (Campolongo et al. 2009b). Consistent with these findings, others have reported that infusion of the CB1 receptor antagonist AM251 into the amygdala (Bucherelli et al. 2006) or hippocampus (de Oliveira Alvares et al. 2005) disrupts the consolidation of long-term memory, possibly by inhibiting long-term potentiation (de Oliveira Alvares et al. 2006)**.** More recently, similar to the effects of glucocorticoids on memory consolidation, we found that endocannabinoid effects on the consolidation of long-term memory of inhibitory avoidance training follow an inverted-U shaped dose–response relationship. Moderate doses enhanced memory whereas both lower and higher doses were less effective (P. Atsak et al. unpublished observation).

Recent studies indicated that baseline arousal levels can influence the sensitivity to cannabinoid drugs in influencing memory processes. For instance, it has been reported that cannabinoid receptor activation differently influences neural processes

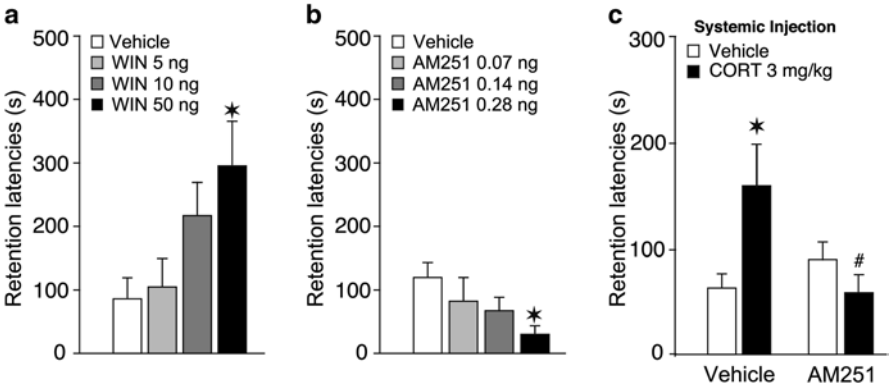

Fig. 5.4 Endocannabinoids in the basolateral complex of the amygdala (BLA) enhance memory consolidation and enable glucocorticoid modulation of memory. **a** Immediately posttraining bilateral intra-BLA infusions of the CB1 receptor agonist WIN55,212-2 (5, 10, 50 ng in 0.2 µL) enhance 48-h inhibitory avoidance retention. **b** Immediate posttraining intra-BLA infusions of the CB1 receptor antagonist AM251 (0.07, 0.14, 0.28 ng in 0.2 µL) impair inhibitory avoidance retention. **c** Immediate posttraining bilateral infusions of AM251 (0.14 ng in 0.2 µL) into the BLA block retention enhancement induced by subcutaneous injections of corticosterone (3 mg/kg, s.c.). Data represent step-through latencies (mean + SEM) in seconds on the 48-h inhibitory avoidance retention test. *$p < 0.05$ versus vehicle; #$p < 0.05$ versus corticosterone group. (Adapted from Campolongo et al. 2009b)

underlying the formation of emotional memory as compared to nonemotional memory (Chhatwal and Ressler 2007; Akirav 2011). We further demonstrated that the endocannabinoid-uptake inhibitor AM404, which enhances endocannabinoid tone, induces different effects on recognition memory performance in rats subjected to different levels of emotional arousal induced by the changes in environmental condition (Campolongo et al. 2012). In agreement with these findings, a recent experiment in humans reported that cannabinoid drugs such as THC also preferentially modulate memory for emotionally arousing, and not mundane, experiences (Ballard et al. 2012). Recently, we investigated cannabinoid effects on both short- and long-term memory of object recognition training under two conditions that differed in their training-associated level of emotional arousal (Campolongo et al. 2013). As shown in Fig. 5.5a, WIN55,212-2 administered immediately after object recognition training to rats that were not previously habituated to the experimental context induced impairment of short-term retention performance. In contrast, the same dose of WIN55,212-2 enhanced short-term memory of rats that had received extensive prior habituation to the experimental context (Campolongo et al. 2013). The effects of posttraining WIN55,212-2 administration on long-term memory of the object recognition training were different. WIN55,212-2 enhanced long-term retention of object recognition memory in nonhabituated rats, but had no effect on long-term memory of extensively habituated rats (Fig. 5.5c and d). This arousal-dependent cannabinoid effect on memory is thus highly comparable to the glucocorticoid effects described earlier and lend support for the idea that the origin of

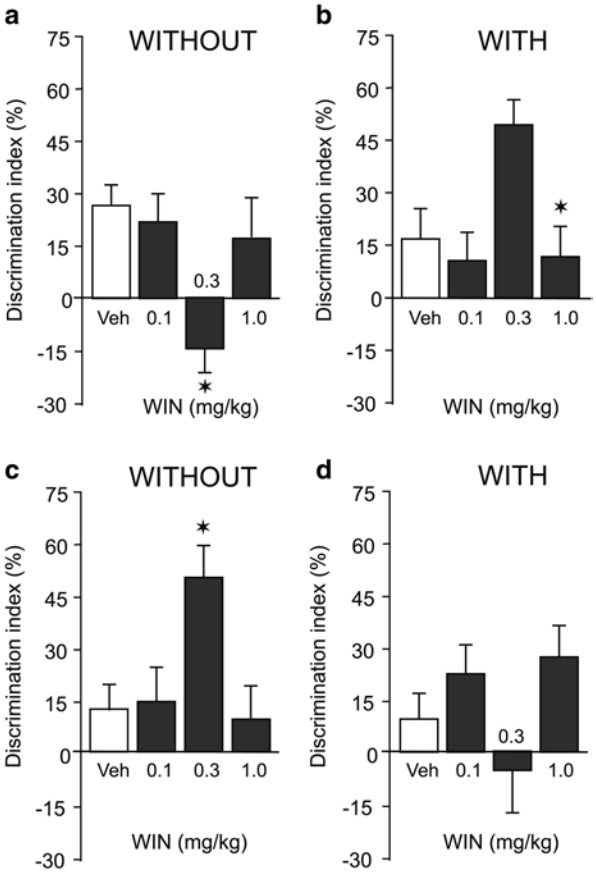

Fig. 5.5 Effects of the CB receptor agonist WIN55,212-2 (*WIN*) on both short- and long-term retention of object recognition are influenced by training-associated emotional arousal. For both experiments, rats were either habituated to the training context for 7 days (*WITH*) or not habituated (*WITHOUT*). On day 8, they were given a 3-min training trial during which they could freely explore two identical objects, training was followed by a systemic administration of WIN 0.1, 0.3, 1.0 i.p. Retention was tested either 1 or 24 h later by placing the rats back into the apparatus for 3 min; in this trial, one object was similar to the training objects whereas the other was novel. Data represent discrimination index (%) on the retention trial, expressed as mean ± SEM. The discrimination index was calculated as the difference in the time spent exploring the novel and the familiar object, expressed as the ratio of the total time spent exploring both objects. Posttraining WIN dose-dependently impaired 1-h object recognition performance of nonhabituated rats **a**, but enhanced object recognition performance of extensively habituated rats **b**. In contrast, posttraining administration of WIN, in a dose that impaired 1-h performance, enhanced 24-h object recognition performance of nonhabituated rats **c**, but not of well-habituated rats **d**. $*p < 0.05$ versus vehicle. (Adapted from Campolongo et al. 2013, with permission)

the altered sensitivity to cannabinoids results from a differential activation of the noradrenergic system during arousing versus low-arousing conditions (Patel and Hillard 2003; Oropeza et al. 2005; Page et al. 2007; Carvalho and Van Bockstaele 2012). Corroborating these findings, cannabinoid drugs have been shown to influence the noradrenergic system by increasing neuronal activity in the locus coeruleus or directly boosting norepinephrine levels in limbic and cortical brain regions (Patel and Hillard 2003; Oropeza et al. 2005; Page et al. 2007).

5.5.3 Role of Endocannabinoids in Mediating Glucocorticoid Effects on Memory Consolidation

Recent evidence consistently points out that glucocorticoids interact with the endocannabinoid system in influencing different brain functions, including learning and memory (Atsak et al. 2012b; Crosby and Bains 2012; Hill and Tasker 2012; Ramot and Akirav 2012; Riebe et al. 2012; de Bitencourt et al. 2013). Some of these studies clearly demonstrated an involvement of the endocannabinoid system in mediating the rapid effects of glucocorticoids (Campolongo et al. 2009b; Hill and McEwen 2009; Evanson et al. 2010; Atsak et al. 2012b; Hill and Tasker 2012). Although the mechanism of how glucocorticoids might exert such rapid actions remains to be clarified, the first evidence for a role of the endocannabinoid system in regulating glucocorticoid effects originated from an elegant series of in vitro studies by Tasker and colleagues. They demonstrated that corticosterone rapidly induces the release of endocannabinoids in the hypothalamus. Endocannabinoids then act retrogradely to inhibit the release of glutamate in the paraventricular nucleus and suppress HPA-axis activity (Di et al. 2003, 2005b). More recently, an in vivo study by Hill et al. (2010) corroborated these findings and showed that a single injection of corticosterone rapidly (within 10 min) elevated AEA levels in the hypothalamus, but also in the amygdala and hippocampus. Collectively, these and other data (Hill and Tasker 2012) suggested that the endocannabinoid system might play a critical role in mediating rapid glucocorticoid effects on the stress response.

In a series of experiments, we sought to examine whether endocannabinoid transmission might play a role in mediating glucocorticoid effects on memory consolidation. For this, rats were trained on an inhibitory avoidance task and received immediate posttraining infusions of the CB1 receptor antagonist AM251 into the BLA together with a systemic administration of corticosterone. As is shown in Fig. 5.4c, intra-BLA administration of the CB1 receptor antagonist blocked the ability of systemic corticosterone to facilitate memory consolidation of inhibitory avoidance training (Campolongo et al. 2009b). Similarly, other researchers found that a CB1 receptor antagonist infused into the hippocampus blocked memory enhancement induced by the synthetic glucocorticoid dexamethasone (de Oliveira Alvares et al. 2010). To investigate whether this glucocorticoid effect on the endocannabinoid system is dependent upon an adrenal steroid receptor on the cell surface, we per-

formed an additional experiment. The CB1 receptor antagonist AM251 infused into the BLA blocked the memory-enhancing effects induced by concurrent infusions of either a specific GR agonist or the membrane-impermeable ligand cort:BSA (P. Atsak et al. unpublished observation). In contrast, the GR antagonist RU38486 infused into the BLA did not alter the memory-enhancing effects of WIN55,212-2. Therefore, these findings indicate that endocannabinoid transmission is required for mediating glucocorticoid effects on memory consolidation, presumably involving the activation of a GR on the cell surface and downstream endocannabinoid signaling. While these findings clearly indicate that endocannabinoids essentially mediate glucocorticoid effects on memory consolidation, they do not address whether the endocannabinoid system mediates the rapid effects of glucocorticoids onto the noradrenergic system. To investigate this issue, we examined whether endocannabinoid effects on memory consolidation might depend on concurrent noradrenergic activity within the BLA. Highly comparable to the above-described effects of glucocorticoids on memory consolidation, the β-adrenoceptor antagonist propranolol administered into the BLA prevented the memory enhancement induced by concurrent administration of the CB receptor agonist WIN55,212-2 (P. Atsak et al. unpublished observation). In an earlier study, we already reported that systemic administration of the endocannabinoid oleoylethanolamide enhances memory consolidation of inhibitory avoidance training. As the β-adrenoceptor antagonist propranolol infused into the BLA blocks this memory enhancement (Campolongo et al. 2009a), these findings indicate that also oleoylethanolamide enhances memory consolidation via a norepinephrine-dependent mechanism in the BLA. These findings are thus in line with previous evidence showing that systemic or local administration of a CB1 receptor agonist increases norepinephrine levels in cortical and limbic brain regions (Oropeza et al. 2005; Page et al. 2007). These findings might not only explain the observation that cannabinoids, like glucocorticoids, preferentially modulate memory of emotionally arousing information, but they also illustrate that the endocannabinoid is a likely target for glucocorticoids in influencing noradrenergic activity in the context of memory consolidation processes.

5.5.4 Role of Endocannabinoids in Mediating Glucocorticoid Effects on Memory Retrieval

As discussed, glucocorticoids induce temporary impairment of the retrieval of memory of previously acquired information (Wolf 2008; de Quervain et al. 2009; Roozendaal et al. 2009a). Importantly, these glucocorticoid effects on memory retrieval are mediated through GRs and, similar to the consolidation effects, essentially depend on arousal-induced noradrenergic activity (Roozendaal et al. 2006a). Highly comparable to glucocorticoid effects, cannabinoid drugs, including THC, induce impairment of memory retrieval (Castellano et al. 2003; Ranganathan and D'Souza 2006). We recently examined whether endocannabinoid signaling within

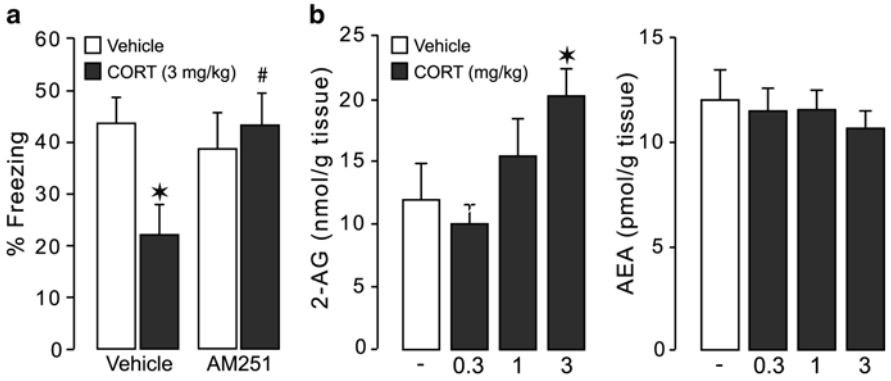

Fig. 5.6 Role of the endocannabinoid system in regulating glucocorticoid effects on retrieval of contextual fear memory. **a** Hippocampal infusion of the CB1 receptor antagonist AM251 (0.35 ng in 0.5 μL) administered 1 h before retention testing blocks the impairment of retrieval of contextual fear memory induced by concurrent systemic corticosterone (*CORT*; 3 mg/kg) treatment. Results represent mean ± SEM. *$p < 0.05$ versus vehicle; #$p < 0.05$ versus corticosterone alone. **b** Systemic corticosterone (0.3, 1, or 3 mg/kg) treatment dose-dependently increased hippocampal 2-AG, but not AEA, levels in the same time window of the retention test. All results represent mean ± SEM. *$p < 0.05$ versus vehicle. (Adapted from Atsak et al. 2012)

the hippocampus is involved in mediating glucocorticoid-induced impairment of retrieval of contextual fear memory. In this experiment, rats were trained on a contextual fear conditioning task and tested 24 h later for fear memory retention (Atsak et al. 2012a). As shown in Fig. 5.6a, we found that a blockade of hippocampal CB1 receptors by local infusions of AM251, 1 h before retention testing prevented the impairing effects of systemically co-administered glucocorticoids on retrieval of contextual fear memory. Moreover, we found that a retrieval-impairing dose of corticosterone elevated hippocampal levels of 2-AG, but not AEA (Fig. 5.6b). As mentioned before, glucocorticoid effects on memory retrieval highly depend on noradrenergic activity, thus in order to determine whether endocannabinoids mediate the effects of glucocorticoids on the noradrenergic system, we further examined possible interactions between the endocannabinoid and noradrenergic systems during retrieval processing of contextual fear memory. We found that the CB receptor agonist WIN55,212-2 infused into the hippocampus 1 h before retention testing impaired the retrieval of contextual fear memory; however, the β-adrenoceptor antagonist propranolol blocked the impairing effect of WIN55,212-2 on memory retrieval (Fig. 5.7a). Conversely, the CB1 receptor antagonist AM251 infused into hippocampus together with an impairing dose of norepinephrine failed to abolish the impairing effect of norepinephrine on memory retrieval (Fig. 5.7b). Collectively, these findings indicate that endocannabinoids interact with the noradrenergic system in inducing memory retrieval impairment and that the noradrenergic system appears to be located downstream, at least functionally, from the endocannabinoid system.

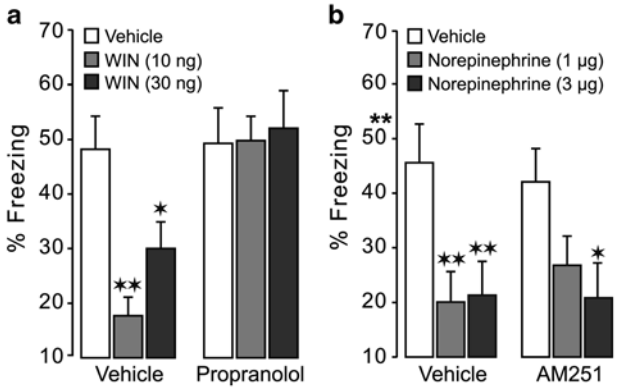

Fig. 5.7 Endocannabinoid and norepinephrine interactions in the dorsal hippocampus on retrieval of contextual fear memory. **a** The CB receptor agonist WIN55,212-2 (WIN, 10 or 30 ng in 0.5 µL) infused into the hippocampus 1 h before the retention test impaired retrieval of contextual fear memory. Concurrent infusion of the β-adrenoceptor antagonist propranolol (1.25 µg) blocked this WIN55,212-2-induced memory retrieval impairment. Results represent mean ± SEM. $*p < 0.05$, $**p < 0.001$ versus vehicle. **b** Intrahippocampal infusions of norepinephrine (1 or 3 µg in 0.5 µL) administered 1 h before the retention testing impaired retrieval of contextual fear memory. Concurrent infusion of the CB1 receptor antagonist AM251 (0.35 ng) did not block this impairment. Results represent mean ± SEM. $*p < 0.05$; $**p < 0.01$ versus vehicle. (Adapted from Atsak et al. 2012a)

5.5.5 The Model

In both the hippocampus and amygdala, CB1 receptors are expressed in GABAergic cells and to a minor extent in glutamatergic cells. Thus, an activation of CB1 receptors can modify the release of both neurotransmitters (Katona et al. 1999, 2001; Azad et al. 2003; Kawamura et al. 2006; Kano et al. 2009). Although our behavioral findings provide strong support for the view that the endocannabinoid system is crucially involved in mediating the fast effects of glucocorticoids on the noradrenergic system in modulating both the consolidation and the retrieval of memory, the underlying mechanism remains unknown. The endocannabinoid system might either directly influence noradrenergic activity or, alternatively, alter noradrenergic function indirectly via a modulation of GABAergic or glutamatergic activity. Within the BLA, CB1 receptors are in particular abundantly expressed in GABAergic interneurons (Katona et al. 2001) and activation of CB1 receptors has consistently been shown to suppress the release of GABA (Katona et al. 1999, 2001; Ohno-Shosaku et al. 2001) via a rapid inhibition of calcium entry into the terminals (Hoffman and Lupica 2000; Wilson et al. 2001). It is well established that the amygdala GABAergic system is involved in memory modulation such that posttraining infusions of GABA receptor antagonists into the BLA enhance memory consolidation, whereas posttraining infusions of GABA receptor agonists impair memory consolidation (McGaugh and Roozendaal 2002). Importantly, the modulatory effects of GABAergic transmission on memory crucially depend on an interaction with

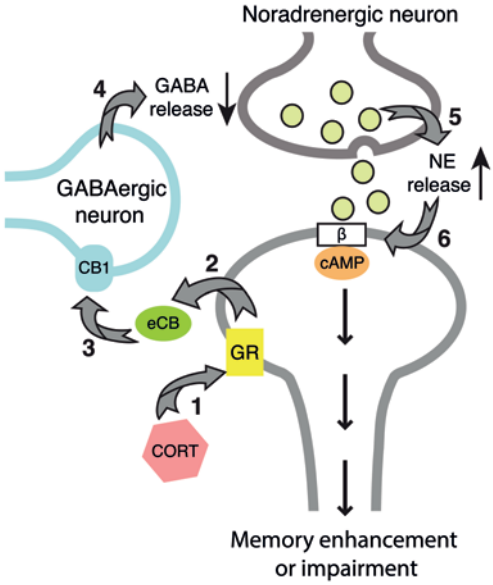

Fig. 5.8 Model on the role of the endocannabinoid system in the BLA in mediating glucocorticoid effects on norepinephrine release in regulating memory consolidation. Corticosterone (*CORT*) is released during training on an emotionally arousing tasks and binds to a membrane-bound glucocorticoid receptor (*GR*) **1**, that activates a pathway to induce endocannabinoid synthesis **2**. Endocannabinoids are then released into the synapse where they bind to CB1 receptors on GABAergic terminals **3** and thereby inhibit the release of GABA **4**. This suppression of GABA release subsequently disinhibits norepinephrine (*NE*) release **5** and this results in an activation of the postsynaptic β-adrenoceptor and the downstream cAMP/PKA/pCREB intracellular signaling pathway **6**. These stress hormone effects on noradrenergic activation in the BLA are required for enhancement of memory consolidation or impairment of memory retrieval. (Adapted from Atsak et al. 2012b, with permission)

the noradrenergic system. A *β*-adrenoceptor antagonist administered systemically or directly into the BLA prevents the modulatory effects of GABAergic drugs on memory consolidation (McGaugh 2004). Moreover, an in vivo microdialysis study indicated that the administration of a GABA receptor antagonist increases norepinephrine levels in the amygdala, whereas that of a GABA receptor agonist decreases norepinephrine levels (Hatfield et al. 1999). Thus, endocannabinoids might increase BLA neuronal activity by decreasing GABAergic neurotransmission, leading to increased noradrenergic activity within the BLA. Interestingly, a recent study indicated that glucocorticoids also increase the excitability of BLA neurons by decreasing the impact of GABAergic influences (Duvarci and Paré 2007).

As shown in Fig. 5.8, corticosterone binds to a membrane-associated GR and induces the release of endocannabinoids. Then, endocannabinoids bind to CB1 receptors and suppress GABAergic transmission that can then result in increased levels of norepinephrine. This increased norepinephrine level is associated with en-

hanced consolidation and temporary impairment of memory recall (McGaugh and Roozendaal 2002). Nevertheless, it is possible that glucocorticoid-induced memory effects might be also a result of endocannabinoid-mediated changes in glutamatergic signaling (Popoli et al. 2011).

5.6 Concluding Remarks

The evidence summarized in this chapter indicates that glucocorticoids enhance memory consolidation while impair memory retrieval in various animal and human memory tasks. Although glucocorticoids may act in many different brain regions to modulate these memory processes, the effects appear to depend critically on arousal-induced BLA activation and noradrenergic neurotransmission within the BLA. These findings may help to explain why glucocorticoids do not uniformly modulate memory for all kinds of information but, rather, preferentially influence the memory of emotionally arousing information. Furthermore, the findings indicate that glucocorticoids do not only modulate memory via their classically recognized genomic actions, but that glucocorticoid interactions with the noradrenergic arousal system depend critically on rapid, nongenomic actions via an activation of membrane-bound GRs and increased endocannabinoid signaling. Future studies will have to determine whether and how such rapid glucocorticoid effects on arousal mechanisms might cooperate with the slow actions in influencing gene transcription and the formation of strong and stabile memories of emotionally significant experiences.

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