Chapter 2
Regulation of Excitatory Synapses by Stress Hormones

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Abstract Shortly after stress, brain levels of many transmitters and hormones such as corticosterone are elevated. In the brain, corticosterone affects those cells that express high-affinity mineralocorticoid receptors (MRs) and/or lower-affinity glucocorticoid receptors (GRs). Principal neurons in the hippocampal cornus ammoni 1 (CA1) area and dentate gyrus abundantly express both MR and GR, while principal cells in the basolateral amygdala have high GR but relatively low MR levels. Neurons in all three areas quickly respond to corticosterone with an enhancement in spontaneous glutamatergic transmission, an effect that is nongenomic and involves MR. This rapid effect is transient in hippocampal cells but sustained in amygdala neurons. The areas differ in their slow gene-mediated response to corticosterone. Hippocampal CA1 cells show an increased current amplitude in response to spontaneously released glutamate-containing vesicles; synaptically evoked responses are generally unaffected. The number of action potentials during a period of depolarization is attenuated, via a slow GR-dependent pathway. By contrast, basolateral amygdala neurons show higher excitability and more efficient transfer of action potentials several hours after corticosteroid exposure. The dichotomy between the two areas could explain why emotional aspects of stressful events are generally better retained than neutral aspects.

Abbreviations

AHP	Afterhyperpolarization
AMPA	α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
BLA	Basolateral amygdala
BSA	Bovine serum albumin
CA1	Cornus ammoni 1
(m)EPSC/EPSP	(Miniature) Excitatory postsynaptic current/potential

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ERK	Extracellular signal-regulated kinase
GR	Glucocorticoid receptor
LTD	Long-term depression
LTP	Long-term potentiation
MEK	Mitogen-activated protein kinase kinase
MR	Mineralocorticoid receptor
NMDA	N-methyl-D-aspartate

2.1 Introduction

When an organism encounters a situation that could (potentially) perturb its homeostatis, this is subjectively experienced as "stress." Two systems are activated upon stress exposure: (1) the autonomic nervous system, which quickly results in release of (nor)adrenaline from the adrenal medulla, but also from neurons in the locus coeruleus and nucleus tractus solitaries (for reviews see Valentino and Von Bockstaehle 2008; McIntyre et al. 2012) and (2) the hypothalamo-pituitary-adrenal axis, which eventually causes synthesis and secretion of corticosteroid hormones from the adrenal cortex (for reviews see De Kloet et al. 2005; Ulrich-Lai and Herman 2009). In humans, cortisol is the primary circulating corticosteroid, while in rodents corticosterone prevails. The stress-induced secretion of corticosteroid hormones occurs on top of ultradian pulses with a 1-h inter-pulse interval (Lightman and Conway-Campbell 2010). The peak of these ultradian pulses varies: low-amplitude pulses are seen at the start of the inactive period, and the amplitude of pulses gradually rises towards the start of the active period. Overall, the pulses give rise to a circadian release pattern of corticosteroid hormones.

Corticosterone easily enters the brain due to its lipophilic character. It reaches every cell in the brain but is only active in those cells that express receptors. Two corticosteroid receptors have been recognized, based on their molecular properties and pharmacological profile (Reul and de Kloet 1985; Evans and Arriza 1989). Low levels of corticosteroid hormones first bind to the mineralocorticoid receptor (MR), which has a Kd of approximately 0.5 nM. Expression levels of MR are high in all hippocampal neurons, as well as neurons in the lateral septum and some motor nuclei in the brain stem. In cortical cells and most of the amygdalar nuclei, MR expression is much lower. The brain MR is structurally similar to MRs in epithelial cells, such as in the kidney (see for review Funder 2010). However, in these cells cortisol and corticosterone are converted by the 11-β-hydroxysteroid dehydrogenase isoform 2 into metabolites with extremely low affinity for the MR, so that MRs become available for binding by the less prevalent hormone aldosterone (Wyrwoll et al. 2011). In most cells in the brain however, the 11-β-hydroxysteroid dehydrogenase isoform 2 is not highly expressed, explaining why corticosterone and cortisol are the main ligands of the brain MR.

With higher concentrations of corticosterone or cortisol, the hormones also bind to the glucocorticoid receptor (GR). This receptor has a Kd of 2–5 nM and is much more ubiquitously expressed (Reul and de Kloet 1985; Weinberger et al. 1985). The corticosteroid concentration reached at the trough of ultradian pulses is lower than the Kd of the GR; therefore, this receptor only becomes substantially occupied at the peak of high-amplitude ultradian pulses and after stress. The difference in Kd of the two receptor types is very relevant for neurons that express MR as well as GR, e.g., pyramidal neurons in the CA1 hippocampal area and granule cells in the dentate gyrus. These cells shuttle between on the one hand a condition of predominant MR activation during the circadian trough, and on the other hand concurrent MR and GR activation after stress or at the peak of high-amplitude ultradian pulses.

MR and GR reside in the cytoplasm when unbound to corticosteroids, in a complex with chaperone molecules such as heat shock proteins (Biddie and Hager 2009). When corticosteroids bind the receptor, the chaperones dissociate and the activated receptors move to the nucleus. There, they either homodimerize and directly bind to glucocorticoid response elements in the DNA; or they bind as monomers to other transcription factors, thus interfering with the efficacy of the latter. Through both pathways, corticosteroid receptors slowly and persistently change the expression of responsive genes, an approximate 2 % of the total (Datson et al. 2008). Potentially, this will alter neuronal function in many ways and for a prolonged period of time.

More recently, though, it has become evident that corticosteroid hormones are also active within minutes, via nongenomic signalling. This was first described extensively for parvocellular neurons in the hypothalamic paraventricular nucleus (Di et al. 2003, 2005). Rapid corticosteroid effects are probably mediated by MRs and GRs located on the plasma membrane rather than in the cytoplasm or nucleus. Although specific receptor molecules mediating fast effects by corticosteroids have been identified in nonmammalian vertebrates (Orchinik et al. 1991), convincing evidence for the existence of receptors exclusively mediating rapid actions was never obtained in rodents. In addition to corticosteroid actions developing over the course of minutes or hours, these hormones also seem to be able to change neuronal function in a third, intermediate time-domain which may depend on posttranslational modifications. For instance, recent evidence supports that GRs change Histone 3 methylation (Roozendaal et al. 2010; Gutièrrez-Mecinas et al. 2011; Hunter et al. 2012), which causes functional effects with a delay of approximately 20 min.

Evidently, variations in corticosteroid level will change the function of many neurons, over a wide range of time, starting directly after stress and lasting for hours to even days (for details see Joëls et al. 2012). In this chapter, we will particularly highlight rapid and slow cellular actions by corticosterone on glutamatergic transmission in three parts of the brain that are important for (emotional) memory formation, i.e., the hippocampal CA1 area, the dentate gyrus, and the basolateral amygdala.

2.2 Rapid effects

2.2.1 Hippocampus

Glutamate is the main excitatory transmitter in the brain. It mainly acts through AMPA and NMDA receptors. Upon arrival of action potentials in the presynaptic terminal, intracellular calcium levels are raised, which in turn promotes the release of glutamate. However, glutamate is to a limited extent also spontaneously released, i.e., in the absence of action potentials. This spontaneous activity can be detected postsynaptically through the recording of so-called miniature excitatory postsynaptic currents (mEPSCs), each of which represents the response to a spontaneously released synaptic vesicle containing glutamate.

CA1 hippocampal pyramidal cells show an enhanced mEPSC frequency during the application of corticosterone, while mEPSC amplitude, rise time, and decay remain unaffected by the hormone (Karst et al. 2005). Corticosterone diminished the second relative to the first evoked response in a paired pulse stimulation paradigm, supporting that the hormone increases the release probability of glutamate-containing vesicles, instead of increasing the number of synaptic contacts. The corticosterone-induced increase in mEPSC frequency is short-lived; when the hormone application is terminated, mEPSC frequency quickly returns to the pretreatment level. Corticosterone was found to exert very similar effects in the presence of a protein synthesis inhibitor, which argues against involvement of a genomic pathway. Corticosterone conjugated to bovine serum albumin (BSA), which does not pass the plasma membrane, caused very similar effects on mEPSC frequency; intracellular administration of corticosterone was ineffective (Karst et al. 2005; Olijslagers et al. 2008). These findings suggest that corticosterone binds to a receptor molecule located on (or close to) the membrane. Based on the just-effective concentration (10 nM), it was thought that these rapid actions of corticosterone involve GRs rather than MRs, similar to what had been reported for hypothalamic neurons (Di et al. 2003). Yet, the selective GR agonist RU 28386 was entirely ineffective, and effects of corticosterone were not blocked by the GR antagonist RU 38486 (Karst et al. 2005). Conversely, 10 nM of the MR agonist aldosterone in the presence of RU 38486 highly effectively increased mEPSC frequency, an effect that was completely blocked by the MR-antagonist spironolactone, indicating that the rapid effects are mediated by MR rather than GR. In agreement, the increased mEPSC frequency by corticosterone was not observed in forebrain specific MR knockouts, but remained intact in GR knockout mice. Recently, it was reported that the MR-mediated increase in mEPSC frequency depends on the expression of limbic system-associated membrane protein, Lsamp (Qiu et al. 2010). Using pharmacological tools it was shown that granule cells in the dentate also display an MR-dependent raise in mEPSC frequency, very similar to that seen in CA1 pyramidal cells (Pasricha et al. 2011).

The pathway through which corticosterone rapidly affects release probability has to some extent been resolved. Rapid effects are blocked by MEK inhibitors,

pointing to involvement of ERK (Olijslagers et al. 2008). ERK activation is known to induce phosphorylation of Synapsin-I which promotes neurotransmitter release (Hilfiker et al. 1998). Interestingly, ERK activation and Synapsin-I were also proposed to be involved in slow GR-dependent modulation of glutamatergic transmission in the hippocampus (Revest et al. 2010). In agreement, ERK is important for stress-induced effects on hippocampus-dependent learning (Reul et al. 2009).

Corticosterone also rapidly changes postsynaptic properties of hippocampal cells, including aspects of glutamatergic transmission. Thus, in the postsynaptic membrane, lateral movement of GluA2 subunits of the AMPA receptor is rapidly increased by corticosterone and is linked to a long-lasting higher dwell-time in the postsynaptic density (Groc et al. 2008). This postsynaptic effect—like the presynaptic effect of corticosterone—involves MRs, is induced by the membrane-impermeable corticosterone-BSA conjugate and is not affected by a protein synthesis inhibitor. Both actions on glutamate transmission are expected to increase the (spontaneous) activity of hippocampal CA1 neurons. Since corticosterone also rapidly reduces the voltage dependent and transient A-current in CA1 neurons (Olijslagers et al. 2008), the changes in glutamatergic transmission are probably accompanied by more sustained firing. Overall, excitatory transmission is thought to be increased shortly after corticosterone reaches the brain.

Findings with regard to a slightly more delayed time-domain (approximately 20–60 min after stress) are more equivocal. One study (Tse et al. 2011) reported that CA1 cells respond more strongly to excitatory input 20–30 min after the start of corticosterone administration. At the single cell level, the NMDA/AMPA ratio was increased, most likely via GR. Extracellularly, an increase in the field excitatory postsynaptic potential evoked via NMDA—but not AMPA—receptors was found. However, most studies report *reduced* responses to synaptic input in this time-domain. For instance, spontaneous firing of hippocampal cells was reduced 20 min after peripheral injection of corticosterone (Pfaff et al. 1971). Various types of stress impaired the stability or reduced the firing rate of hippocampal place cells in this intermediate time-domain (Kim et al. 2007; Passecker et al. 2011). In vitro administered corticosterone (at a very high dose) was found to reduce the population spike amplitude in the CA1 area, reaching a plateau 20–40 min after corticosterone administration was started (Vidal et al. 1986). Also, the ability to evoke an action potential through synaptic stimulation and the amplitude of the EPSP in CA1 neurons declined with repeated stimulation of the afferents (Joëls and de Kloet 1993); these effects became evident approximately 20 min after the start of corticosterone administration. In neonatal cultured hippocampal neurons, corticosterone was found to reduce NMDA-evoked currents, through a membrane-bound receptor not blocked by classical MR- or GR-antagonists (Liu et al. 2007; Zhang et al. 2012).

The overall impact of corticosterone on CA1 pyramidal cell activity not only depends on its effect on excitatory transmission but also on inhibitory transmission. Corticosterone does change GABAergic inhibitory transmission in the intermediate time-domain, but the effects are variable and seem to depend on the recording method (Zeise et al. 1992; Teschemacher et al. 1996; Hu et al. 2010). Interestingly, inhibitory signals, i.e., spontaneous inhibitory postsynaptic current amplitude, were

reported to be enhanced in the dorsal hippocampus via GRs (Maggio and Segal 2009), while in the ventral hippocampus an MR-dependent reduction in spontaneous inhibitory postsynaptic current frequency was reported. These effects were seen >25 min after onset of corticosterone administration and peaked at 55 min.

All in all, most studies agree that corticosterone quickly increases spontaneous glutamatergic transmission. Synaptically evoked field potentials, however, were mostly not rapidly altered by corticosterone administration (e.g., Wiegert et al. 2006; Pu et al. 2007). Of course, it should be realized that in this rapid time-window other transmitters and hormones released by stress are also active and will affect the excitability. For instance, noradrenaline acting via β-adrenoceptors (but not α-adrenoceptors) increases excitatory transmission (see, e.g., Gereau and Conn 1994; Croce et al. 2003; Zhou et al. 2012), a phenomenon that in the dentate gyrus was shown to involve Synapsin-I phosphorylation (Parfitt et al. 1991). The neuropeptide *corticotropin-releasing hormone* (CRH) is known to quickly potentiate population spikes in the CA1 hippocampal area evoked by Schaffer collateral stimulation (Blank et al. 2002). Therefore, enhanced hippocampal activity during this phase directly after stress probably prevails. After this initial phase, that is 20–60 min after corticosterone reaches hippocampal cells, mostly inhibitory actions have been reported.

2.2.2 Basolateral Amygdala

Corticosterone rapidly increases mEPSC frequency of principal cells in the BLA, similar to what has been described for neurons in the CA1 area and dentate gyrus (Karst et al. 2010). However, in contrast to the latter regions, mEPSC frequency in BLA cells remains high, even after washout of the hormone. While the onset is clearly too fast to involve genomic signalling, the persistence of the response was found to depend on protein synthesis and requires expression of both MR and GR (Karst et al. 2010). The sustained response to a first pulse of corticosterone changes BLA cell properties such that they show a *reduced* mEPSC frequency in response to a second pulse of corticosterone. In contrast to the rapid response to the first corticosteroid exposure, the response to a second pulse was shown to involve GRs and the cannabinoid receptor-1. These rapid inhibitory responses were also seen when animals were first exposed to stress and subsequently to a pulse of corticosterone in vitro. The reversal in response depending on the recent stress history of the organism was called metaplasticity (Karst et al. 2010; see Fig. 2.1). One explanation for the shift in responsiveness after the second exposure to corticosterone is a change in the number of MR and/or GR located on the membrane, e.g., caused by internalization of MRs after the first pulse of corticosterone. Obviously, this needs further investigation.

The functional relevance of the quick increase in spontaneous excitatory transmission induced by corticosterone in BLA neurons is still unclear. Both at the single cell and the field potential level, corticosterone did not quickly change AMPA- or NMDA-R mediated synaptic responses (Liebmann et al. 2009; Pu et al. 2009).

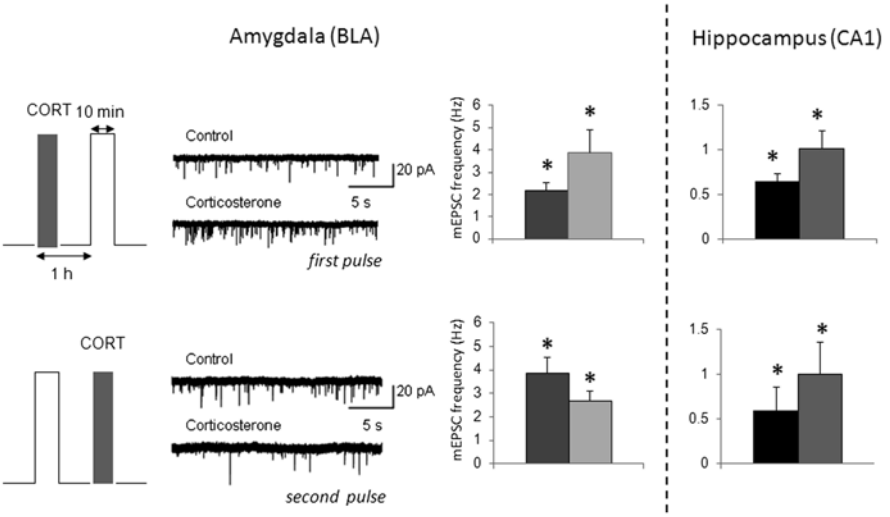

Fig. 2.1 In principal neurons of the *BLA*, a single pulse of corticosterone (*CORT*) (10 min, 100 nM) causes an increase in mEPSC frequency (*top left; dark bar:* mean mEPSC frequency prior to corticosterone application; *light grey bar:* mean mEPSC frequency during corticosterone application). The mEPSC frequency remains high even after wash-out (*bottom left*). Against this background, a second pulse of corticosterone decreases mEPSC frequency. By contrast, the response of hippocampal *CA1* neurons to a second pulse (*bottom right*) is highly comparable to the response to the first pulse (*top right*)
* indicates $p < 0.05$

However, as in the hippocampus, the rapid effect of corticosterone on spontaneous glutamatergic transmission may add to the overall change in excitability caused by other stress mediators like noradrenaline or CRH.

2.3 Delayed effects

2.3.1 Hippocampus

Passive or active membrane properties of dorsal CA1 pyramidal neurons, such as resting membrane potential, input resistance or characteristics of the action potential, are generally not much affected over the course of time after application of corticosterone (e.g., Joëls and de Kloet 1989; Kerr et al. 1989; but see Beck et al. 1994). However, neurons in the ventral-most (20%) part of the hippocampus gradually become more excitable after corticosterone application (Maggio and Segal 2009).

Excitability could also be affected via corticosteroid actions on voltage-dependent ion channels. In the dorsal CA1 area corticosterone most prominently changes voltage-dependent calcium currents, much more so than sodium or potassium currents. A series of experiments showed that corticosterone or stress enhances the

amplitude of sustained high-voltage-activated calcium currents in a slow manner, i.e., with a delay of > 1 h (Kerr et al. 1992; Karst et al. 1994; Joëls et al. 2003). The enhancement in calcium current amplitude requires protein synthesis and DNA-binding of GR homodimers (Kerr et al. 1992; Karst et al. 2000). Corticosterone seems to target particularly L-type calcium currents, possibly through transcriptional regulation of β4 subunits (Chameau et al. 2007). Surprisingly, β4 subunits were also transcriptionally regulated by corticosterone in dentate granule cells, but this was not translated to the protein level, nor did corticosterone enhance calcium current amplitude in granule cells (Van Gemert et al. 2009).

The increased calcium influx in CA1 neurons after stress or corticosterone exposure has consequences for downstream calcium-dependent pathways. For instance, depolarization of CA1 neurons leads to calcium influx, which subsequently activates a slow calcium-dependent potassium current, slowing down the transfer of action potentials. Upon termination of the depolarization, this current is slowly deactivated which results in a lingering afterhyperpolarization (AHP). High levels of corticosterone or glucocorticoids were found to enhance the AHP amplitude in CA1 pyramidal neurons recorded 1–4 h later and attenuated the transfer of action potentials during a period of depolarization (Joëls and de Kloet 1989; Kerr et al. 1989; Liebmann et al. 2008). Transfer of longer periods of excitatory information through the CA1 area is thus hampered 1–4 h after corticosterone levels are elevated. As with the passive and active membrane properties, the ventral-most part of the hippocampus reacted oppositely to the dorsal part after corticosterone application, showing *reduced* firing frequency accommodation and more spikes upon depolarization, i.e., higher excitability (Maggio and Segal 2009).

A third pathway through which corticosterone slowly changes excitability in the CA1 hippocampal area concerns its actions on spontaneous glutamatergic transmission. In both CA1 and (unidentified) cultured hippocampal neurons, a pulse of corticosteroids or of selective GR agonists increases the amplitude but not frequency of mEPSCs recorded several hours after corticosteroid exposure (Karst and Joëls 2005; Martin et al. 2009). This increase in amplitude is associated with a slow GR-dependent increase in surface expression of GluA2 subunits (Fig. 2.2) via a process requiring protein synthesis. At the same time the mobility of GluA2 subunits is enhanced (Groc et al. 2008; Martin et al. 2009). These effects on mEPSC amplitude develop > 1 h after corticosterone application and reach a maximal value between 150 and 200 min after onset of hormone treatment (Karst and Joëls 2005; Groc et al. 2008; Martin et al. 2009). Functionally, the increase in mEPSC amplitude occludes chemically induced LTP (Groc et al. 2008; Martin et al. 2009; Xiong et al., unpublished observations), while activity-dependent decreases in synaptic AMPA receptors (long-term depression, LTD) are facilitated.

How these effects on spontaneous glutamatergic transmission impact on synaptically evoked responses is presently unclear. Extracellularly recorded field potentials in the various hippocampal areas were in most studies not reported to be altered by corticosterone or stress (e.g., Pavlides et al. 1996; Bramham et al. 1998; Zhou et al. 2000; Yamada et al. 2003; Chen et al. 2010), although occasionally enhanced (Kavushansky et al. 2006; Avital et al. 2006) or reduced activity was observed

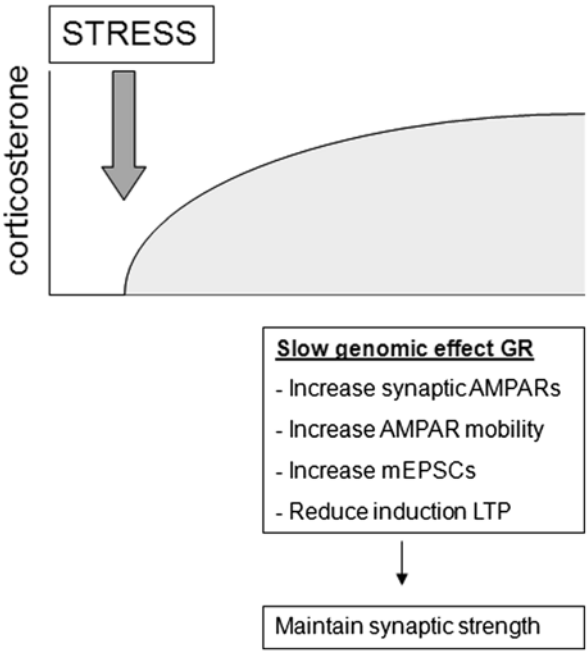

Fig. 2.2 Corticosterone slowly, via a genomic and glucocorticoid receptor (*GR*)-mediated action, enhances α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (*AMPAR*) synaptic transmission. At the same time—possibly via occlusion—corticosterone hampers the ability to strengthen synapses, which may promote the consolidation of relevant information. *mEPSC* miniature excitatory postsynaptic current, *LTP* long-term potentiation

(Hirata et al. 2008). Most likely, corticosteroid actions on excitatory (or inhibitory) transmission are restricted to a limited number of synapses and thus not discerned at a more global level, similar to what has been found after learning (Whitlock et al. 2006). It may also relate to the dose of corticosterone that was used or the intensity of the stressor. This is suggested by a study of Rey et al. (1987), showing that low doses of corticosterone enhance the amplitude of the population spike evoked by synaptic stimulation in the CA1 area, while high doses decrease the population spike.

2.3.2 Basolateral Amygdala

In the BLA, administration of a brief pulse of corticosterone increased input resistance and resulted in a more depolarized membrane potential of principal neurons some hours later (Duvarci and Pare 2007). This was only seen in a subpopulation of neurons with a very high input resistance (Duvarci and Pare 2007; Liebmann et al. 2008). In contrast to the CA1 area, firing frequency accommodation and AHP amplitude in the BLA were unaffected or even reduced by corticosterone (Duvarci and Pare 2007; Liebmann et al. 2008). Possibly, the low expression of alpha1.3 calcium channel subunits in the BLA contributes to this lack of modulation in firing frequency accommodation and AHP amplitude (Liebmann et al. 2008), despite a clear GR-dependent increase in sustained high-voltage-activated calcium currents (Karst et al. 2002). Corticosterone furthermore shifted the reversal potential

of GABA-receptor linked chloride channels to more depolarized potentials, causing reduced IPSP amplitude upon synaptic stimulation. Altogether, these effects are expected to slowly enhance the excitability of BLA neurons after a single pulse of corticosterone. This has indeed been demonstrated at the field potential level some hours (but not a day; see Rodriguez Manzanaers et al. 2005) after restraint stress, elevated platform stress or corticosterone injection, both in vivo and in vitro (Kavushansky and Richter-Levin 2006; Kavushansky et al. 2006). In conclusion, slow effects of corticosterone on principal cells in the BLA differ from responses in the dorsal CA1 area and, rather, resemble responses in the ventral-most CA1 region.

2.4 Concluding remarks

Electrophysiological studies over the past decades have supplied evidence that directly after stress corticosteroid hormones may affect neuronal excitability differently than some hours later. In the hippocampus, spontaneous glutamatergic transmission is quickly and transiently enhanced by corticosterone. Some hours later, the number of GluA2 subunits in the plasma membrane is increased which is associated with enhanced mEPSC amplitudes. This indicates that spontaneous glutamatergic transmission is quickly enhanced and through another mechanism may remain elevated in those synapses that were involved in the initial response to stress. How these changes in spontaneous glutamatergic transmission translate to the transfer of information through the CA1 area or dentate gyrus is presently hard to predict. It is conceivable that glutamatergic transmission in some synapses is considerably facilitated in a similar manner as seen after high-frequency stimulation. However, when a series of (glutamate-mediated) signals reaches CA1 neurons >20 min after corticosterone exposure, the transfer of excitatory transmission is suppressed rather than enhanced. This may explain why it is difficult to induce long-term potentiation (LTP) at that time (see for review Kim and Diamond 2002). All of these actions may serve to enhance the signal-to-noise ratio and preserve stress-related information earlier encoded in the hippocampus.

Corticosteroid hormones affect transmission in the ventral-most part of the hippocampus and the BLA in a different manner than in the dorsal hippocampus. Neurons in, e.g., the BLA are quickly excited when corticosterone levels rise, but (different from dorsal hippocampal cells) both the spontaneous glutamatergic transmission and the response to multiple action potentials remain enhanced, also hours after the first exposure to corticosterone. This suggests that in the ventral-most part of the hippocampus and BLA the window for encoding of stress-related information is more prolonged than in the dorsal hippocampus. Given the role of the BLA in the processing of emotional information, this observation may explain why emotional aspects of a stressful situation are strongly retained, much more so than neutral aspects which particularly involve the dorsal hippocampus (Buchanan and Lovallo 2001; Kuhlmann and Wolf 2006; Van Stegeren et al. 2010), although not all studies report this (Abercrombie et al. 2003; Rimmele et al. 2003).

How the metaplasticity in responses to corticosterone, as described for the BLA, will impact on the signal transfer through this area after stress, is at this time hard to predict. To really appreciate the functional relevance of all of these changes recorded in brain slices, it will be necessary to focus on in vivo recordings, preferably in freely moving animals. This is technically demanding, certainly if one wants to correlate firing patterns of many cells in multiple regions of the brain. Nevertheless, such in vivo recordings will be necessary to understand how corticosteroid modulation of glutamatergic transmission can alter behavior in the aftermath of stress.

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