Chapter 8
Stress Modulation of Synaptic Plasticity in the Hippocampus

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Abstract Despite its homogeneous, highly ordered structure, the hippocampus serves very different functions along its septo-temporal axis; while the dorsal (septal) end is associated with cognition, its ventral (temporal) region regulates emotion and anxiety. As stress has been known to affect cognitive functions in the brain, it is of prime interest to try and understand how the hippocampus assumes its cognitive roles under stressful conditions. We hypothesize that stress switches the focus of control of hippocampal functions by differential modulation of synaptic plasticity in the dorsal and ventral sectors of the hippocampus through the activation/suppression of steroid hormones and monoamine neurotransmission. Herein, we will review recent studies on the effects of stress on synaptic plasticity in the dorsal and ventral hippocampus and outline the outcomes of this modulation on stress-related global functions of the temporal lobe, which hosts the hippocampus. We propose that steroid hormones act as molecular switches to change the strength of synaptic connectivity in the hippocampus following stress, thus regulating the routes by which the hippocampus is functionally linked to the rest of the brain. This role has profound implications for the pathophysiology of psychiatric disorders.

Abbreviations

CRH	Corticotropin releasing hormone
DH	Dorsal hippocampus
iGR	Intracellular glucocorticosterone receptors
iMR	Intracellular mineralocorticosterone receptors
LTP	Long term potentiation
mGluR	Metabotropic glutamate receptor
mGR	Membrane glucocorticosterone receptor
mIPSC	Miniature inhibitory post synaptic currents

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mMR   Membrane mineralocorticosterone receptors
VGCC   Voltage gated calcium current
VH   Ventral Hippocampus

8.1   Introduction: The Hippocampus, more than One?

The view of the hippocampus, the most intensively studied brain structure, has changed drastically over the past century. Considered part of the Papez circuit, the hippocampus was originally related to affective circuits in the brain. The striking observation of loss of short-term memory in epileptic patients undergoing hippocampectomy, led to a series of animal studies testing the hypothesis that the hippocampus is a locus of short-term storage of memories. This enthusiasm about the role of the hippocampus in memory neglected the fact that some of these patients had little cognitive deficits, but suffered from severe emotional problems following the operation. Only more recent studies began to appreciate the significant role of the ventral hippocampus (VH) in emotion and anxiety, distinctly different from the more traditional role of the dorsal hippocampus (DH) in cognitive functions. This assertion is based on lesion and stimulation studies as well as recording of single neurons in freely moving animals, and on studies in hippocampal slice preparations. Indeed, there are distinct differences in the distribution of synaptic proteins between the two poles of the hippocampus. While the roles of the two regions of the hippocampus in cognitive versus affective functions becomes evident (see below), there are still unsolved issues related to this distinction. First, why is it so important to have two major brain functions in one rather small structure. Second, while the hippocampus has a lamellar organization, meaning that the entire input/output pathway is embedded in parallel lamella along the septo-temporal axis, it does contain extensive longitudinal fiber systems that unite the entire hippocampus into one apparent functional unit. Since the VH and the DH have different connections with the rest of the brain, with the DH projecting mainly to cortical structures, whereas the VH mainly to the amygdala and hypothalamus, it is apparent that the weight of connectivity of the hippocampus may switch between the dorsal and ventral poles, in relation to the ambient state of the animal. The factors that determine this switch and the rules that govern them will be discussed below.

## 8.2   Corticosteroid receptors in the brain

Steroid hormones have been traditionally associated with regulation of peripheral organs, associated with stress (corticosterone) or with gonadal function (estrogen and androgens). Over the years, it became evident that these hormones also act within the hypothalamus, in a feedback regulatory loop, to affect the release of the

neural factors that modulate production of the steroid hormones. More recently, several observations have elucidated new roles of steroid hormones in modulating higher CNS functions. Specifically, both stress and steroid hormones have been shown to affect synaptic receptors and ion channels and therefore regulate synaptic transmission and neuronal plasticity in several different ways. Furthermore, corticosterone is not the only player in the control of stress responses, and the central factor that regulates it, corticotropin releasing hormone (CRH) has been described to exert an important role in modulating neuronal plasticity in the hippocampus and elsewhere (Joels and Baram 2009). Consequently, stress hormones have been implicated in processes ranging from homeostatic to cognitive functions. Likewise, in some disorders of the nervous system, hormones have been shown to play critical roles: favoring or halting the disease process. Thus, the interaction between peripheral hormones and central networks seem to be more intense than ever before.

In the present study, we review current knowledge on the effects of steroid hormones on synaptic plasticity and define their influence on cognitive and emotional functions of the DH and VH.

Following the exposure to stressful stimuli, the steroid hormone corticosterone (cortisol in humans) is released from the adrenal glands in order to set up the best response to the challenge by acting on steroid receptors (de Kloet et al. 2005). These are distributed throughout the body and have a particularly dense distribution in the CNS (de Kloet et al. 2005). In the brain, the cellular and molecular targets for the action of corticosterone include, in addition to basic metabolic processes, an effect on excitatory (Karst and Joels 2005) and inhibitory (Maggio and Segal 2009a, b) synaptic transmission, as well as an effect on voltage-gated calcium channels (VGCC) (Karst et al. 2000; Chameau et al. 2007). These effects are mediated by the activation of mineralocorticoid receptors (MRs) and glucocorticoid receptors (GRs) (Joels 1999; de Kloet et al. 2005; Joels 2008, Joels et al. 2008). Initially, it was suggested that both receptors act as nuclear transcription factors that modify protein synthesis and produce a slow, persistent change in the function of the cell (de Kloet et al. 1993, 2008). More recently, the existence of a new family of membrane-bound MR and GR (mMR and mGR, respectively), which act through novel nongenomic pathways, has been reported (Karst et al. 2005; de Kloet et al. 2008). In this route, mMR and mGR can rapidly affect ionic conductances and thereby modify cell excitability and function (Karst et al. 2005; de Kloet et al. 2008). These membrane-bound receptors appear to differ from their intracellular cognates, not only in their location on the cell membrane, but also in their molecular structures (Joels et al. 2008), in their affinities for corticosterone, and in their downstream mechanisms of action which involve activation of G proteins (Joels et al. 2008). Specifically, intracellular MR (iMR) have a very high affinity for corticosterone and are highly expressed in all hippocampal subfields, as well as in cells of the central amygdala, lateral septum, and some motor nuclei in the brainstem (Joels 2006). Intracellular GR (iGR) have a relatively low affinity, are widely distributed throughout the brain, and are expressed both in neurons and in glia (Joels 2006). Consequently, it has been proposed that iMR hardly participates, if at all, in the fast response to stressful stimuli, due to their characteristic of being already saturated by the low ambi-

Fig. 8.1 Schematic of the hippocampus and its connections with the main efferent systems. While the dorsal hippocampus is connected with cortical structures, e.g., prefrontal and retrosplenial cortex (PRCx and RsCx, respectively), the VH is linked to the amygdala and ventromedial nucleus of the hypothalamus (VMH). *Blue* indicates the main functional connections at rest and *red* the main functional connections during stress.
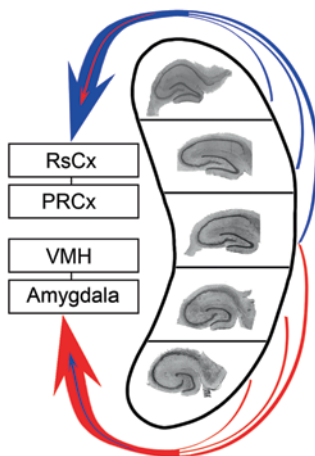
ent levels of corticosterone at rest (Joels 2006, 2008). Conversely, iGR have been reported to become gradually activated by rising levels of corticosterone following a stressful event (Joels 2006, 2008) (Fig. 8.1). Therefore, under physiological conditions, cells that co-express both receptor types, such as principal cells in the CA1 region, the dentate gyrus (DG), and the central amygdala, will shift between predominant iMR activation and concurrent mMR and iGR activation (Joels and Krugers 2007).

8.3   The Hippocampus: One structure, two functions?

The realization that there might be intrinsic differences between CA1 neurons of the DH and VH, which may underlie the differences in their firing properties as well as their ability to undergo plastic changes, led to several attempts to characterize the biophysical properties of CA1 neurons in the two sectors. The first study, by Maggio and Segal (2009a) reported that neurons in the two sectors had similar resting potentials, input resistance and membrane time constant, but the VH neurons generated fewer action potentials to a depolarizing current pulse than DH neurons. A more recent study (Dougherty et al. 2012) reported opposite results, with the VH neurons being more depolarized by 7 mV than the DH neurons, a difference that resulted in more action potential discharges to the same depolarizing current pulse. In a more recent study, they propose (Dougherty et al. 2013, Marcelin et al. 2012) that VH neurons have different compositions of HCN channels, responsible for Ih in these neurons. This might underlie the 7 mV depolarization and the higher input resistance of their VH CA1 neurons and eventually explain the difference in excitability between the two studies. Notably, if the VH neurons would be more excitable, then a larger amplitude theta rhythm is expected to be generated in this area. However, theta rhythm of smaller amplitude compared to their cognates in

DH has been reported (Patel et al. 2012). In addition, a different excitability of the CA1 neurons in the two regions should generate larger response amplitudes to Schaffer's collateral stimulation in VH cells compared to DH neurons. However, several experiments have shown that both DH and VH have similar input/output relations (Papatheodoropoulos and Kostopoulos 2000; Grigoryan et al. 2012). Altogether these studies suggest that there is a genuine difference in synaptic plasticity between DH and VH.

Several other hippocampal features are affected by stress differently in the DH and VH. For example, neurogenesis is one of the unique properties of the DG of the hippocampus, one of two locations in the brain where adult neurogenesis was characterized (O'Leary et al. 2012). VH neurogenesis is more affected by stress than DH, and drugs that reduce the effects of stress are active primarily in the VH (Felice et al. 2012, Xia et al. 2012, Tanti et al. 2012, Hawley and Leasure 2012, Hawley et al. 2012). This difference may be related to different regulation of brain derived neurotrophic factor (BDNF), which has been linked to neurogenesis, to depression and to the DH/VH disparity (Roth et al. 2011). Furthermore, stress-induced memory impairments involve different steroid receptors in DH and VH (Dorey et al. 2012), and stimulation of the VH ameliorates fear memory (Cleren et al. 2013). Also, exercise facilitates recovery from stress-induced protein synthesis decline in VH (Daniels et al. 2012). Finally, the VH is more sensitive to redox dysregulation than the DH, and the difference is reflected in GABAergic interneurons as well as electrical activity (Steullet et al. 2010).

These and other studies indicate that the DH and VH may react to stressful stimulation in a different manner, and thus, a careful analysis of the direct effect of stress and corticosterone in the VH and DH is justified.

8.4   Corticosteroid receptors in the regulation of hippocampal LTP

The identification of the molecular cascades of corticosteroids actions in the brain resulted in a series of studies examining the role of corticosterone in neuronal plasticity as well as in the cellular mechanisms underlying learning and memory such as long-term potentiation (LTP) and long-term depression (LTD) (Bliss and Collingridge 1993). Initial studies indicated that induction of LTP in the hippocampal area CA1 is impaired in a rat exposed to behavioral stress, such as inescapable shock (Foy et al. 1987; Shors et al. 1989). Administration of high doses of corticosterone either in vivo (Diamond et al. 1992) or in vitro (Pavlides et al. 1996; Alfarez et al. 2002) mimicked this effect, indicating that corticosterone is likely to mediate this action of stress. Specifically, corticosterone-induced impairment of LTP seems to be due to the activation of iGR, which depresses NMDA receptors (Calabrese et al. 2012) and NMDA-dependent LTP (Krugers et al. 2005) (Fig. 8.1b). Conversely, it was also shown that LTP could be enhanced in the presence of low-to-moderate concentrations of corticosterone, while in absence of corticosterone LTP

induction was impaired (Diamond et al. 1992). These studies show that the effects of corticosteroids on LTP induction are dose-dependent and follow an inverted U-shaped curve (Fig. 8.1) (Diamond et al. 1992; Joels 2006).

Further studies, however, have presented a more complex view on the effects of steroid hormones on synaptic plasticity. Specifically, it seems that the same dosage of corticosterone that impairs NMDA-dependent LTP can in fact enhance VGCC-dependent LTP (Krugers et al. 2005). This species of LTP is found in the amygdale where it is believed to underlie the formation of fear memories (Blair et al. 2001; Bauer et al. 2002) and can be evoked in the hippocampus as well (Borroni et al. 2000) (Fig. 8.1b). Interestingly, in the hippocampus, corticosterone appears to enhance VGCC LTP through an iGR-dependent mechanism (Krugers et al. 2005). It has been proposed that this effect requires a genomic pathway, as it occurs after a long delay between the exposure to stress and/or corticosterone and the recordings (Krugers et al. 2005), thus probably depending on the binding of GR homodimers to DNA that causes an increase in calcium currents (Karst and Joels 2005; Chameau et al. 2007). Recent data from our group have shown that MRs are also able to enhance VGCC LTP (Maggio and Segal 2007b): either stress or physiological concentrations of corticosterone can enhance LTP in the VH, while inhibiting it in the DH (Maggio and Segal 2007b). In particular, corticosterone enhances LTP through MRs since a selective MR agonist, aldosterone, shares the same effect in the VH (Maggio and Segal 2007b). The proposed mechanism excludes an interaction between MR and NMDA receptors, as aldosterone by itself does not increase NMDA-dependent synaptic potentials (Maggio and Segal 2007b). Conversely, MR-induced LTP can be blocked by nifedipine, suggesting that VGCCs are likely responsible for this effect (Maggio and Segal 2007b) (Fig. 8.1b). It is likely that MR activates VGCC by modulating ionic conductances or changing VGCC activation kinetics. In vivo experiments have shown that MR activation is able to increase LTP in the DH as well (Avital et al. 2006). Specifically, animals which were injected with a GR antagonist prior to the stressful exposure, such that only MR could be activated by stress, show a much larger LTP than controls. In contrast, those animals previously injected with an MR antagonist and then exposed to stress, allowing only GR activation, show a much lower LTP than controls (Avital et al. 2006). These recordings were performed in the DG and even though there could be differences in the effects of stress and steroids between the DG and CA1 (Joels and Krugers 2007), MRs were still shown to mediate an enhancement of LTP.

These experiments raise several issues. It could be argued that the experiments in the VH were conducted using an in vitro preparation where ambient corticosterone maintained normally through the circulation is washed out. Consequently, MRs are not occupied in the slice, and are ready to be activated by the superfused drug and produce LTP enhancement in the VH. This might not reflect the situation in the intact animal, where the brain is constantly exposed to fluctuating concentrations of corticosterone. In fact, MR should be already saturated by the resting concentration of corticosterone and should not respond to the stress-induced rise of corticosterone in the presence of a GR blockade. This, however, does not seem to be the case (Avital et al. 2006). Furthermore, even though both MRs and GRs are

expressed in the VH, corticosterone action is mediated by activation of MR rather than GR. This reflects the observation that in the VH, MR concentration is double that of GR (Robertson et al. 2005). If so, according to the U-shaped curve model of corticosterone effects, MR should be saturated faster by the rising concentration of corticosterone and their effect should fade away faster in favor of the slower GR activation. This is in contrast with the experimental evidence. Altogether, it seems that the simple, dose-dependent, inverted U-shaped curve does not fully explain the modulatory functions of MR and GR on LTP in the different sectors of the hippocampus, therefore calling for the involvement of other factors.

A possible mechanism that may clarify the MR-dependent enhancement of LTP should take into consideration the activation of mMR (Fig. 8.1). These receptors act through a faster mechanism (de Kloet et al. 2008) and have lower affinities for corticosterone compared to their intracellular cognates (Joels 2008) and similar to that of the iGR (Joels 2008). In addition, MR activation enhances LTP in the VH within 1 h, too short time window to be accounted for by activation of genomic mechanisms (Joels and Krugers 2007; Joels 2008), but compatible with the faster time course of the nongenomic routes. Thus, mMR could be the preferential target for rising concentrations of corticosterone in the VH if one takes into account the similar affinities for corticosterone between mMR and iGR, and the denser distribution of the former over the latter (Robertson et al. 2005) (Fig. 8.1a, b).

MRs are likely to enhance LTP through activation of VGCC. In our experiments, we could not detect any effect of iGR on VGCC LTP. This could most likely be due to the shorter time window of observation in our experiments compared to those done by others (Krugers et al. 2005). In any case, both MR and GR were reported to increase VGCC LTP (Krugers et al. 2005; Maggio and Segal 2007b). This apparent contrast could probably be explained by considering the different time courses of MR and GR enhancement of VGCC LTP. Specifically, MR has an earlier effect than GR and it could be that in the VH stress mediates a fast enhancement of LTP by MR followed by a second, slow increase in LTP due to GR activation. This proposal is compatible with the proposed role of the VH as a key player in the pathway that conveys stressful information to the hypothalamus and the amygdale so as to organize the stress response (Fig. 8.2) (Moser and Moser 1998; Maggio and Segal 2010; Segal et al. 2010).

8.5 Corticosteroid regulation of hippocampal functions

The regulation of LTP by corticosterone in the hippocampus has profound system implications. Following stress, the quick MR-mediated increase in LTP facilitates the flow of the information related to stress from the VH to the ventral hypothalamus and other lower brain centers, so that the autonomic response to stress can be organized. Later on, the MR-mediated response fades away and the effect of GR dominates. As previously mentioned, GR enhancement of VGCC LTP has been shown to have a role in the formation of fear memories in the amygdale (Blair et al.
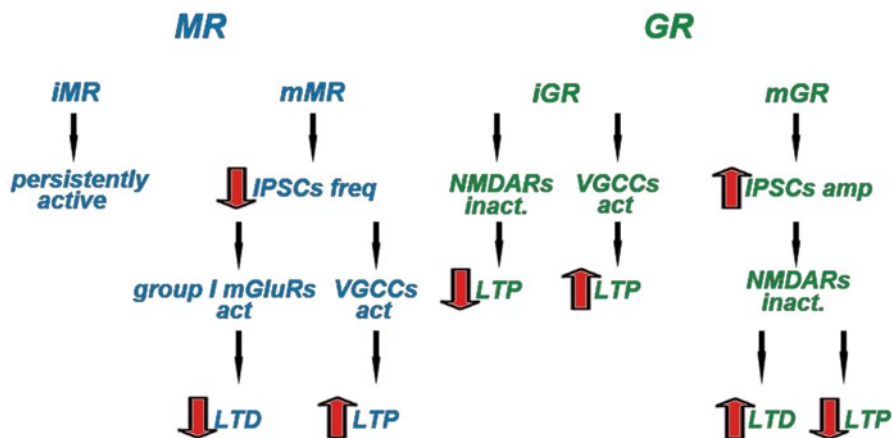
Fig. 8.2 Summary diagram of the main corticosterone effects in the hippocampus, there are intracellular mineralocorticosterone receptors (*iMR*), membrane mineralocorticosterone receptors (*mMR*), and the same for glucocorticosterone receptors (*GR*). Each receptor type has specific effects on the ability of CA1 neurons in the hippocampus to undergo long-term potentiation (*LTP*) in response to afferent stimulation. *MR* mineralocorticoid receptors, *IPSC* inhibitory postsynaptic currents, *LTD* long-term depression, *VGCC* voltage-gated calcium current, *mGluR* metabotropic glutamate receptor, *iGR* intracellular glucocorticosterone receptors, *NMDAR* N-methyl-D-aspartate receptor, *mGR* membrane glucocorticosterone receptor

2001; Bauer et al. 2002). In this respect, GR could play the same function in the VH: the formation of the memory for the stressful event at the VH-amygdala pathway. Indeed, the evidence that MR and GR act on the same mechanism can have different purposes due to the time window of the respective outcomes that take place. Considering this, it could be interesting to study the relationship between the MR and GR responses in the VH.

In the DH, the reduction of LTP is likely to be mediated by GR (Maggio and Segal 2007b). This effect seems to occur in less than 1 h, a relatively quick response that is unlikely to be mediated by a genomic mechanism. GR could reduce NMDA-mediated LTP either by a direct or an indirect mechanism. As far as it concerns the indirect mechanism hypothesis, we have demonstrated that a GR agonist, dexamethasone, increases IPSCs and mIPSCs amplitude in the DH within 10 min (Maggio and Segal 2009a, 2012), consistent with the possible activation of mGR. Therefore, the increase in GABAA conductance could hyperpolarize the membrane, thus preventing the cell from reaching the threshold of depolarization that unlocks NMDA receptors from the Mg2+ block (Fig. 8.1b). All in all, our experiments indicate that GR affect LTP through a fast, probably nongenomic mechanism. Even though this hypothesis needs to be explored further, the fast suppression of LTP in the DH can underlie the switch in the weight between the DH and VH; by reducing DH LTP and simultaneously enhancing LTP in the VH, the stressful stimuli could temporarily suppress the cognitive route of the hippocampus to cortical structures and enable the transmission of the emotional information through the VH to the amygdala.

Conversely, LTD induction is facilitated by behavioral stress, through a mechanism that requires GR (Pavlides et al. 1995; Xu et al. 1997; Xu et al. 1998) and their effect on NMDA receptors (Kim et al. 1996; Yang et al. 2005). We replicated previous experiments where both stress and corticosterone facilitate LTD through a GR-dependent mechanism in the DH, but we have also shown that LTD is impaired in the VH through a MR-dependent mechanism (Maggio and Segal 2009b). Specifically in the latter case, LTD is transformed into a slow-onset LTP following the exposure to stressful stimulation (Maggio and Segal 2009b). As is the case for LTP, changes in LTD either in the DH or VH were observed at approximately 1 h after the exposure to the stress, a time window that could be compatible with non-genomic mechanisms. The MR-induced conversion of LTD to LTP in the VH could be due to the activation of VGCC, which will further facilitate the ventral route to the amygdale (Fig. 8.1b). Group I mGluR have been shown to enhance LTD in CA1 (Fitzjohn et al. 2001; Rammes et al. 2003), but, interestingly, they have been reported to induce a slow-onset potentiation in the DG (Manahan-Vaughan and Reymann 1996). In a previous study, we showed that, in the VH, application of DHPG, a group I mGluR agonist, increases the population spike amplitude in response to a baseline stimulation (Maggio and Segal 2007a). Taken together, these observations suggest that in the VH, a decrease in GABAergic inhibition can shift LTD to a slow-onset LTP through a group I mGluR-mediated mechanism (Fig. 8.1b).

Corticosteroid regulation of synaptic plasticity in the hippocampus is affected by several factors. An inverted U-shape effect of corticosterone mainly refers to the activation of intracellular corticosteroid receptors and does not count the contribution of membrane-bound steroid receptors. In fact, mMR, which bears a similar corticosterone affinity to that of iGR, will be activated at similar steroid concentrations. This implies that the effect of mMR appears earlier than that of iGR, thus inducing an enhancement of LTP instead of LTD. This might be the case in the VH. An additional factor to be considered is the distribution of MR and GR in specific brain areas, and the ratio of membrane-bound to intracellular receptors expressed therein. This is because at the same affinity value for corticosterone concentration, the receptor that is highly expressed will lead the effects on synaptic plasticity. Another issue that has to be considered is the clusters of brain areas that are involved in a particular stress situation. Various brain regions have specific properties and are incorporated into unique networks, so that even if corticosterone evokes the same effect at the single cell level, this would not always result in the same effect on network functions such as LTP. For instance, both CA1 pyramidal neurons and granule cells in the DG highly express MR as well as GR (Joels 2007, 2008). In the DH, corticosterone and stress consistently suppress the induction of CA1 LTP in vivo and in vitro, unlike the case for the DG. High concentration of corticosteroid (Pavlides et al. 1993) or tail shocks (Shors and Dryver 1994) can indeed suppress LTP; however, in other situations, either no effect (Bramham et al. 1998; Gerges et al. 2001; Alfarez et al. 2003) or enhancement of LTP has been reported (Kavushansky et al. 2006). This is because LTP in the DG seems to be more dependent on indirect inputs from the amygdale (Akirav and Richter-Levin 2002; Kavushanski et al. 2006, Kavushanski and Richter-Levin 2006). Finally, the response to a stressor

is also determined by the history of the organism. For instance, the induction of LTP is impaired in animals that have been exposed to repetitive stress in the weeks prior to the experiment, even if corticosterone levels, at the time of LTP induction, are compatible with the expression of a normal LTP (Alfarez et al. 2003). Studies on the effect of maternal care on synaptic plasticity report that animals that received very little maternal care have poor LTP when they are adult, as opposed to animals that received high maternal care (Champagne et al. 2008). Interestingly, while LTP is suppressed by corticosterone in the latter group, it is enhanced in the former (Champagne et al. 2008).

Long-term effects of stress can produce changes in hippocampal morphology, in addition to an immediate effect on ability to express LTP. For example, Silva-Gomez et al. (2012) found that chronic (5 days) exposure to dexamethasone, a GR agonist, caused a significant reduction in dendritic spine density, primarily in the VH, which was also associated with a shrinkage of dendritic length in these neurons. Thus, the VH appears to be more susceptible to stress than the DH. Another interesting recent difference between DH and VH is in the effects of corticosterone to increase serotonin neurotransmission. Once again, this effect is restricted to the VH (Barr and Forster 2011). Likewise, it has been shown before that physical exercise can counteract the effect of maternal separation. Once again, enhanced locomotion in this experiment has a significant effect to increase synaptic markers only in the VH (Hescham et al. 2009).

Finally, a recent study describes a differential effect of acute stress on glutamate receptors in the DH and VH: while acute stress causes a reduced glutamate synaptic efficacy in the prefrontal cortex and the DH, it causes an augmented glutamate receptor activity in the amygdala and VH (Caudal et al. 2010). This observation complements our proposal for a stress-induced shift in hippocampal control from the DH to the VH (Fig. 8.2). Whether the primary effect of stress is mediated by modulation of the excitatory or the inhibitory synaptic tone in the two sectors of the hippocampus remains to be determined, but evidence for both possibilities has been presented recently. On the other hand, Marrocco et al. (2012) describe a reduction in glutamate release in VH following prenatal stress. Whether these results are congruent with the previous ones remain unclear. These actions may have to do with differences in mode of induction of stress, age of the animals, different receptor distribution, but may also reflect difference in intrinsic properties of the VH neurons compared to the DH counterparts.

8.6 Summary

All in all, corticosteroid modulation of synaptic plasticity in the hippocampus seems to be more complex than previously thought. Additional factors related to the unique spatio-temporal organization of the hippocampus, the different subsets of receptors and intrinsic properties of neurons in the different sectors and their connectivity with the rest of the brain are critical in finalizing the role of stress

in neuronal plasticity. Furthermore, the definition of the borders of the VH is not precise, and different studies range from the bottom half of the hippocampus, to the bottom 1/5th of it. Likewise, stress is defined differently in different studies, and it may cause different levels of transient and sustained elevation of corticosterone, which may affect the observed estimation of the role of stress in neuronal plasticity. Thus, a careful evaluation of the regions and specific neurons tested, the behavioral and physical parameters tested and the time course of expected effects should allow a more reliable progress in the understanding of the role of 'stress' in neuronal plasticity. As it may turn out, there may be more than two hippocampi in one structure, and the possibility of three has been proposed recently (Fanselow and Dong 2010). Further studies will elucidate these issues with respect to hippocampal functions.

References

Akirav I, Richter-Levin G. Mechanisms of amygdala modulation of hippocampal plasticity. J Neurosci. 2002;22(22):9912–21.

Alfarez DN, Wiegert O, Joels M, Krugers HJ. Corticosterone and stress reduce synaptic potentiation in mouse hippocampal slices with mild stimulation. Neuroscience. 2002;115:1119–26.

Alfarez DN, Joels M, Krugers HJ. Chronic unpredictable stress impairs long-term potentiation in rat hippocampal CA1 area and dentate gyrus in vitro. Eur J Neurosci. 2003;17(9):1928–34.

Avital A, Segal M, Richter-Levin G. Contrasting roles of corticosteroid receptors in hippocampal plasticity. J Neurosci. 2006;26:9130–4.

Barr JL, Forster GL Serotonergic neurotransmission in the ventral hippocampus is enhanced by corticosterone and altered by chronic amphetamine treatment. Neuroscience. 2011;182:105–14.

Bauer EP, Schafe GE, Ledoux JE. NMDA receptors and L-type voltage-gated calcium channels contribute to long-term potentiation and different components of fear memory formation in the lateral amygdala. J Neurosci. 2002;22:5239–49.

Blair HT, Schafe GE, Bauer EP, Rodrigues SM, Ledoux JE. Synaptic plasticity in the lateral amygdala: a cellular hypothesis of fear conditioning. Learn Mem. 2001;8:229–42.

Bliss TV, Collingridge GL. A synaptic model of memory: long-term potentiation in the hippocampus. Nature. 1993;361:31–9.

Borroni AM, Fichtenholtz H, Woodside BL, Teyler TJ. Role of voltage-dependent calcium channel long-term potentiation (LTP) and NMDA LTP in spatial memory. J Neurosci. 2000;20:9272–6.

Bramham CR, Southard T, Ahlers ST, Sarvey JM. Acute cold stress leading to elevated corticosterone neither enhances synaptic efficacy nor impairs LTP in the dentate gyrus of freely moving rats. Brain Res. 1998;789(2):245–55.

Calabrese F, Guidotti G, Molteni R, Racagni G, Mancini M, Riva MA. Stress-induced changes of hippocampal NMDA receptors: modulation by duloxetine treatment. Neurosci Lett. 2012;521(1):20–5.

Caudal D, Godsil BP, Mailliet F, Bergerot D, Jay TM. Acute stress induces contrasting changes in AMPA receptor subunit phosphorylation within the prefrontal cortex, amygdala and hippocampus. PLoS ONE. 2010;5(12):e15282.

Chameau P, Qin Y, Spijker S, Smit AB, Joels M. Glucocorticoids specifically enhance L-type calcium current amplitude and affect calcium channel subunit expression in the mouse hippocampus. J Neurophysiol. 2007;97:5–14.

Champagne DL, Bagot RC, van Hasselt F, Ramakers G, Meaney MJ, de Kloet ER, Joels M, Krugers H. Maternal care and hippocampal plasticity: evidence for experience-dependent struc-

tural plasticity, altered synaptic functioning, and differential responsiveness to glucocorticoids and stress. J Neurosci. 2008;28:6037–45.

Cleren C, Tallarida I, Guiniec EL, Janin F, Nachon O, Canini F, Spennato G, Moreau JL, Garcia R. Low-frequency stimulation of the ventral hippocampus facilitates extinction of contextual fear. Neurobiol Learn Mem. 2013;101:39–45.

Daniels WM, Marais L, Stein DJ, Russell VA. Exercise normalizes altered expression of proteins in the ventral hippocampus of rats subjected to maternal separation. Exp Physiol. 2012;97(2):239–47.

De Kloet ER, Oitzl MS, Joels M. Functional implications of brain corticosteroid receptor diversity. Cell Mol Neurobiol. 1993;13:433–55.

De Kloet ER, Joels M, Holsboer F. Stress and the brain: from adaptation to disease. Nat Rev Neurosci. 2005;6:463–75.

de Kloet ER, Karst H, Joels M. Corticosteroid hormones in the central stress response: quick-and-slow. Front Neuroendocrinol. 2008;29:268–72.

Diamond DM, Bennett MC, Fleshner M, Rose GM. Inverted-U relationship between the level of peripheral corticosterone and the magnitude of hippocampal primed burst potentiation. Hippocampus. 1992;2:421–30.

Dorey R, Piérard C, Chauveau F, David V, Béracochéa D. Stress-induced memory retrieval impairments: different time-course involvement of corticosterone and glucocorticoid receptors in dorsal and ventral hippocampus. Neuropharmacology. 2012;63(8):1380–8.

Dougherty KA, Islam T, Johnston D. Intrinsic excitability of CA1 pyramidal neurones from the rat dorsal and ventral hippocampus. J Physiol. 2012;590(Pt 22):5707–22.

Dougherty KA, Nicholson DA, Diaz LM, Buss EW, Neuman KM, Chetkovich DM, Johnston D. Differential expression of HCN subunits alters voltage-dependent gating of h-channels in CA1 pyramidal neurons from the dorsal and ventral hippocampus. J Neurophysiol. 2013;109:1940–53.

Fanselow MS, Dong HW. Are the dorsal and ventral hippocampus functionally distinct structures? Neuron. 2010;65(1):7–19.

Felice D, O'Leary OF, Pizzo RC, Cryan JF. Blockade of the GABA(B) receptor increases neurogenesis in the ventral but not dorsal adult hippocampus: relevance to antidepressant action. Neuropharmacol. 2012 63:1380–8

Fitzjohn SM, Palmer MJ, May JE, Neeson A, Morris SA, Collingridge GL. A characterisation of long-term depression induced by metabotropic glutamate receptor activation in the rat hippocampus in vitro. J Physiol. 2001;537:421–30.

Foy MR, Stanton ME, Levine S, Thompson RF. Behavioral stress impairs long-term potentiation in rodent hippocampus. Behav Neural Biol. 1987;48:138–49.

Gerges NZ, Stringer JL, Alkadhi KA. Combination of hypothyroidism and stress abolishes early LTP in the CA1 but not dentate gyrus of hippocampus of adult rats. Brain Res. 2001;922(2):250–60.

Grigoryan G, Korkotian E, Segal M. Selective facilitation of LTP in the ventral hippocampus by calcium stores. Hippocampus. 2012;22(7):1635–44.

Hawley DF, Leasure JL. Region-specific response of the hippocampus to chronic unpredictable stress. Hippocampus. 2012;22(6):1338–49.

Hawley DF, Morch K, Christie BR, Leasure JL. Differential response of hippocampal subregions to stress and learning. PLoS ONE. 2012;7(12):e53126.

Hescham S, Grace L, Kellaway LA, Bugarith K, Russell VA. Effect of exercise on synaptophysin and calcium/calmodulin-dependent protein kinase levels in prefrontal cortex and hippocampus of a rat model of developmental stress. Metab Brain Dis. 2009;24(4):701–9.

Joels M. Effects of corticosteriod hormones in the hippocampus. Acta Physiol Scand. 1999;167:A3.

Joels M. Corticosteroid effects in the brain: U-shape it. Trends Pharmacol Sci. 2006;27:244–50.

Joels M. Functional actions of corticosteroids in the hippocampus. Eur J Pharmacol. 2008;583:312–21.

Joels M, Krugers HJ. LTP after stress: up or down? Neural Plast. 2007;2007:93202.

Joels M, Karst H, Derijk R, De Kloet ER. The coming out of the brain mineralocorticoid receptor. Trends Neurosci. 2008;31:1–7.

Joëls M, Baram TZ. The neuro-symphony of stress. Nat Rev Neurosci. 2009;10(6):459–66.

Karst H, Joels M. Corticosterone slowly enhances miniature excitatory postsynaptic current amplitude in mice CA1 hippocampal cells. J Neurophysiol. 2005;94:3479–86.

Karst H, Karten YJ, Reichardt HM, De Kloet ER, Schutz G, Joels M. Corticosteroid actions in hippocampus require DNA binding of glucocorticoid receptor homodimers. Nat Neurosci. 2000;3:977–8.

Karst H, Berger S, Turiault M, Tronche F, Schutz G, Joels M. Mineralocorticoid receptors are indispensable for nongenomic modulation of hippocampal glutamate transmission by corticosterone. Proc Natl Acad Sci U S A. 2005;102:19204–7.

Kavushansky A, Richter-Levin G. Effects of stress and corticosterone on activity and plasticity in the amygdala. J Neurosci Res. 2006;84(7):1580–7.

Kavushansky A, Vouimba RM, Cohen H, Richter-Levin, G, et al. Activity and plasticity in the CA1, the dentate gyrus, and the amygdala following controllable vs. uncontrollable water stress. Hippocampus. 2006;16(1):35–42.

Kim JJ, Foy MR, Thompson RF. Behavioral stress modifies hippocampal plasticity through N-methyl-D-aspartate receptor activation. Proc Natl Acad Sci U S A. 1996;93:4750–3.

Krugers HJ, Alfarez DN, Karst H, Parashkouhi K, Van Gemert N, Joels M. Corticosterone shifts different forms of synaptic potentiation in opposite directions. Hippocampus. 2005;15:697–703.

Maggio N, Segal M. Unique regulation of long term potentiation in the rat ventral hippocampus. Hippocampus. 2007a;17(1):10–25.

Maggio N, Segal M. Striking variations in corticosteroid modulation of long-term potentiation along the septotemporal axis of the hippocampus. J Neurosci. 2007b;27:5757–65.

Maggio N, Segal M. Differential corticosteroid modulation of inhibitory synaptic currents in the dorsal and ventral hippocampus. J Neurosci. 2009a;29:2857–66.

Maggio N, Segal M. Differential modulation of long-term depression by acute stress in the rat dorsal and ventral hippocampus. J Neurosci. 2009b;29:8633–8.

Maggio N, Segal M. Corticosteroid regulation of synaptic plasticity in the hippocampus. ScientificWorldJournal. 2010;10:462–9.

Maggio N, Segal M. Stress and corticosteroid modulation of seizures and synaptic inhibition in the hippocampus. Exp Neurol. 2012;234:200–7.

Manahan-Vaughan D, Reymann KG. Metabotropic glutamate receptor subtype agonists facilitate long-term potentiation within a distinct time window in the dentate gyrus in vivo. Neuroscience. 1996;74(3):723–31.

Marcelin B, Lugo JN, Brewster AL, Liu Z, Lewis AS, McClelland S, Chetkovich DM, Baram TZ, Anderson AE, Becker A, Esclapez M, Bernard C. Differential dorso-ventral distributions of Kv4.2 and HCN proteins confer distinct integrative properties to hippocampal CA1 pyramidal cell distal dendrites. J Biol Chem. 2012;287(21):17656–61.

Marrocco J, Mairesse J, Ngomba RT, Silletti V, Van Camp G, Bouwalerh H, Summa M, Pittaluga A, Nicoletti F, Maccari S, Morley-Fletcher S. Anxiety-like behavior of prenatally stressed rats is associated with a selective reduction of glutamate release in the ventral hippocampus. J Neurosci. 2012;32(48):17143–54.

Moser MB, Moser EI. Functional differentiation in the hippocampus. Hippocampus. 1998;8:608–19.

O'Leary OF, O'Connor RM, Cryan JF. Lithium-induced effects on adult hippocampal neurogenesis are topographically segregated along the dorso-ventral axis of stressed mice. Neuropharmacology. 2012;62(1):247–55.

Papatheodoropoulos C, Kostopoulos G. Decreased ability of rat temporal hippocampal CA1 region to produce long-term potentiation. Neurosci Lett. 2000;279(3):177–80.

Patel J, Fujisawa S, Berényi A, Royer S, Buzsáki G. Traveling theta waves along the entire septotemporal axis of the hippocampus. Neuron. 2012;75(3):410–7.

Pavlides C, Watanabe Y, McEwen BS. Effects of glucocorticoids on hippocampal long-term potentiation. Hippocampus. 1993;3(2):183–92.

Pavlides C, Kimura A, Magarinos AM, Mcewen BS. Hippocampal homosynaptic long-term depression/depotentiation induced by adrenal steroids. Neuroscience. 1995;68:379–85.

Pavlides C, Ogawa S, Kimura A, Mcewen BS. Role of adrenal steroid mineralocorticoid and glucocorticoid receptors in long-term potentiation in the CA1 field of hippocampal slices. Brain Res. 1996;738:229–35.

Rammes G, Palmer M, Eder M, Dodt HU, Zieglgansberger W, Collingridge GL. Activation of mGlu receptors induces LTD without affecting postsynaptic sensitivity of CA1 neurons in rat hippocampal slices. J Physiol. 2003;546(Pt 2):455–60.

Robertson DA, Beattie JE, Reid IC, Balfour DJ. Regulation of corticosteroid receptors in the rat brain: the role of serotonin and stress. Eur J Neurosci. 2005;21:1511–20.

Roth TL, Zoladz PR, Sweatt JD, Diamond DM. Epigenetic modification of hippocampal Bdnf DNA in adult rats in an animal model of post-traumatic stress disorder. J Psychiatr Res. 2011;45(7):919–26.

Segal M, Richter-Levin G, Maggio N. Stress-induced dynamic routing of hippocampal connectivity: a hypothesis. Hippocampus. 2010;20:1332–8.

Shors TJ, Dryver E. Effect of stress and long-term potentiation (LTP) on subsequent LTP and the theta burst response in the dentate gyrus. Brain Res. 1994;666(2):232–8.

Shors TJ, Seib TB, Levine S, Thompson RF. Inescapable versus escapable shock modulates long-term potentiation in the rat hippocampus. Science. 1989;244:224–22.

Silva-Gómez AB, Aguilar-Salgado Y, Reyes-Hernández DO, Flores G. Dexamethasone induces different morphological changes in the dorsal and ventral hippocampus of rats. J Chem Neuroanat. 2012. pii: S0891-0618(12)00080-4.

Steullet P, Cabungcal JH, Kulak A, Kraftsik R, Chen Y, Dalton TP, Cuenod M, Do KQ. Redox dysregulation affects the ventral but not dorsal hippocampus: impairment of parvalbumin neurons, gamma oscillations, and related behaviors. J Neurosci. 2010;30(7):2547–58.

Tanti A, Rainer Q, Minier F, Surget A, Belzung C. Differential environmental regulation of neurogenesis along the septo-temporal axis of the hippocampus. Emotion. 2012;12(1):58–68.

Xia L, Deloménie C, David I, Rainer Q, Marouard M, Delacroix H, David DJ, Gardier AM, Guilloux JP. Ventral hippocampal molecular pathways and impaired neurogenesis associated with 5-HT$_1$A and 5-HT$_1$B receptors disruption in mice. Neuropharmacology. 2012;63(3):374–84.

Xu L, Anwyl R, Rowan MJ. Behavioural stress facilitates the induction of long-term depression in the hippocampus. Nature. 1997;387:497–500.

Xu L, Holscher C, Anwyl R, Rowan MJ. Glucocorticoid receptor and protein/RNA synthesis-dependent mechanisms underlie the control of synaptic plasticity by stress. Proc Natl Acad Sci U S A. 1998;95:3204–8.

Yang CH, Huang CC, Hsu KS. Behavioral stress enhances hippocampal CA1 long-term depression through the blockade of the glutamate uptake. J Neurosci. 2005;25:4288–93.