Chapter 11
Acute Stress Disrupts Short- and Long-Term Patterns of Synaptic Plasticity in Dorsal Hippocampus and Subiculum: Implications for Hippocampal Output and Behaviour

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Abstract A period of acute stress has complex effects on hippocampal-dependent cognition in the minutes and hours following its occurrence. The neural mechanisms mediating these effects have been the focus of intense investigation for the past several decades. Much of this research has examined the role of acute stress-induced changes in long-term synaptic plasticity in the CA1 region of the dorsal hippocampus. However, numerous experiments demonstrate that acute stress also impairs short-term plasticity in the hippocampus. In addition, the effects of acute stress on short- and long-term plasticity in the dorsal subiculum, the main output area of the hippocampus, has recently been explored. The goals of this chapter are to thoroughly review these data and integrate them with theories regarding the mechanisms underlying the effects of acute stress on hippocampal-dependent cognition. We conclude that acute stress-induced alterations in synaptic plasticity at both CA1 and subiculum synapses likely contribute to the effects of acute stress on declarative-like learning and memory.

Abbreviations

AMPA	α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid
BDNF	Brain derived neurotrophic factor
CA	Cornu Ammonis
Cort	Corticosterone
GR	Glucocorticoid receptor
HPC	Hippocampus
HPA	Hypothalamic-pituitary-adrenal
LDP	Late developing potentiation
LE	Long-Evans

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LTP	Long-term potentiation
LTD	Long-term depression
MR	Mineralocorticoid receptor
N/C	No change
NMDA	*N*-methyl-D-aspartate
PPF	Paired pulse facilitation
SD	Sprague Dawley

11.1 Introduction

In 2008, Howland co-wrote a review paper relating the effects of acute stress on hippocampal synaptic plasticity to learning and memory (Howland and Wang 2008). It focused on the effects of acute stress on *long-term* synaptic plasticity, principally in the Cornu Ammonis (CA)1 subregion. As reviewed in that paper and numerous others (Kim and Diamond 2002; Shors 2004; Joels et al. 2006; Kim et al. 2006; Diamond et al. 2007; Collingridge et al. 2010; Cazakoff et al. 2010; Schwabe et al. 2012), there is strong evidence to support the role of altered long-term potentiation (LTP) and long-term depression (LTD) in the effects of acute stress on cognition, particularly hippocampal-dependent learning and memory. However, the effects of acute stress on patterns of *short-term* hippocampal synaptic plasticity have also been demonstrated in a number of different laboratories (Zhou et al. 2000; Commins et al. 2001; Karst et al. 2005; Gao et al. 2008; Cazakoff and Howland 2010; MacDougall and Howland 2013a;b). These observations raise questions regarding: (1) the exclusive role of altered long-term synaptic plasticity in the effects of acute stress on cognition and (2) whether distinct forms of cognition are disturbed by the effects of acute stress on short-term hippocampal synaptic plasticity. The present review will integrate findings related to short-term synaptic plasticity into existing theories regarding the effects of acute stress on hippocampal-dependent learning and memory. In addition, the effects of acute stress on synaptic plasticity in the subiculum, arguably the major output of the hippocampus (Naber et al. 2000; Behr et al. 2009; O'Mara et al. 2009), have been largely neglected in previous reviews. Thus, the acute stress effects on synaptic plasticity in the CA1 and subiculum regions will be compared.

11.2 Acute Stress

The term stress has been used historically to describe the rather vague range of perceived stimuli or conditions that disturb an organism's homeostasis (Kim and Diamond 2002). While physical threats are commonly considered stressful, psychological aspects of an organism's experience of given stimuli or conditions, such as level

of aversiveness or controllability, are also critical in determining whether a given experience is perceived as "stressful" (Kim and Diamond 2002). Stress causes rapid physiological changes in the body and brain that enable organisms to overcome short periods of challenge; however, chronic stress exposure has negative effects on a number of physiological systems (McEwen and Sapolsky 1995; Sapolsky 2000). Exposure to stress results in activation of the hypothalamic-pituitary-adrenal (HPA) axis leading to the release of glucocorticoid hormones (cortisol in humans; corticosterone in most rodents) from the adrenal glands as well as the release of other mediators such as catecholamine neurotransmitters and cytokines (Herman et al. 2005; Joels and Baram 2009). In the brain, these signalling molecules activate their respective receptors, which produce an array of functional changes such as alterations in synaptic activity, dendritic organization, and neurogenesis (de Kloet et al. 2005; Kim et al. 2006; Howland and Wang 2008; Holmes and Wellman 2009). One brain region that is particularly responsive to acute stress and critically involved in regulating the responsiveness of the HPA axis to acute stress is the hippocampus (Herman et al. 2005).

This review will focus on findings concerning the effects of acute stress on hippocampal synaptic plasticity and related cognitive processes within minutes to hours of the acute stressor. Such effects are the result of short-term changes in the functionality of existing neural circuits prior to the structural remodelling of circuits that occurs in the hours-days following stress. We will also focus on the role of corticosterone in mediating these effects via actions on its two known receptors subtypes: the high-affinity mineralocorticoid receptors (MRs) and lower affinity (approximately tenfold) glucocorticoid receptors (GRs; de Kloet et al. 2005; Joels and Baram 2009; Joels et al. 2012). Both receptor subtypes are expressed in the dorsal hippocampus and subiculum, with expression of MRs particularly high and GR expression more moderate (Reul and de Kloet 1985). Evidence suggests that signalling by MRs and GRs occurs through classical genomic mechanisms and more recently appreciated non-genomic mechanisms to regulate the brain's responsiveness to activation of the HPA axis (Tasker et al. 2006; Joels et al. 2012). As will be discussed below, both of these modes of action are likely involved in regulating the effects of acute stress on synaptic plasticity and learning and memory.

11.3 Hippocampal Synaptic Plasticity

The mammalian hippocampal formation consists of several anatomically distinct subregions including the entorhinal cortex, dentate gyrus, hippocampus proper (CA3 and CA1 subfields), and subiculum (O'Mara et al. 2001; Andersen et al. 2006; van Strien et al. 2009). Standard anatomical views hold that a number of major glutamatergic pathways direct information flow through the hippocampal formation (Andersen et al. 2006; van Strien et al. 2009). Accordingly, highly integrated sensory information from entorhinal cortex (layer II) arrives at dentate gyrus via the perforant path or the CA3 and CA1 regions via the temporoammonic pathway

(Behr et al. 2009; van Strien et al. 2009). Dentate gyrus granular cells direct information to CA3 neurons via the mossy fibers which in turn project to the CA1 region through the Schaffer collaterals. Lastly, CA1 pyramidal cells project either directly back to the entorhinal cortex or to a topographically organized projection to subiculum (Amaral et al. 1991; O'Mara et al. 2001; Andersen et al. 2006). The majority of subicular cells conserve their topographic input along the transverse axis from CA1 and transmit information to the deep layers (layers V and VI) of entorhinal cortex (van Strien et al. 2009), although notable reciprocal projections to other cortical areas also exist (Naber et al. 2001; Behr et al. 2009; O'Mara et al. 2009). Thus, both CA1 and subiculum function as major output structures for the hippocampal formation and are therefore integral for hippocampal-cortical information processing (Naber et al. 2000; Behr et al. 2009; O'Mara et al. 2009). Given availability of experimental data, the effects of acute stress on synaptic plasticity in the monosynaptic Schaffer collateral-CA1 and CA1-subiculum pathways will be the focus of the following discussion.

The characteristics and molecular mechanisms of synaptic plasticity in the hippocampal formation have been intensely investigated given the hypothesized role of synaptic plasticity in normal cognition and brain disorders (Citri and Malenka 2008; Howland and Wang 2008; Collingridge et al. 2010). In this review, a distinction will be drawn between *short-term synaptic plasticity*, plasticity lasting for milliseconds to minutes (Zucker and Regehr 2002), and *long-term synaptic plasticity*, plasticity lasting for hours to days or longer (Martin et al. 2000; Collingridge et al. 2010). A number of models of short- and long-term synaptic plasticity are routinely studied in the rodent hippocampus using in vitro and in vivo electrophysiological recording techniques (Citri and Malenka 2008). Paired pulse facilitation (PPF) is one of the most commonly studied models of short-term plasticity; furthermore, several reports suggest that mechanisms consistent with PPF have an integral role in cognitive processing and memory (Cao and Leung 1991; Silva et al. 1996; Matilla et al. 1998; Dobrunz and Stevens 1999; Ferguson et al. 2004; Kushner et al. 2005). Paired pulse facilitation refers to an increase in the evoked amplitude of the second field potential following the application of two stimuli in close succession (~10–200 ms apart) (Zucker and Regehr 2002; Citri and Malenka 2008). Synapses in both the Schaffer collateral-CA1 and CA1-subiculum pathways exhibit PPF under normal recording conditions (Cazakoff and Howland 2010; MacDougall and Howland 2013a;b). The mechanisms underlying PPF are complex and difficult to specify directly, although residual presynaptic calcium from the first stimulus increasing the probability of neurotransmitter (glutamate) release to the second stimulus is likely involved (Zucker and Regehr 2002; Citri and Malenka 2008).

The most well-characterized models of long-term synaptic plasticity are LTP, a persistent increase in synaptic potential, and LTD, a persistent decrease in synaptic potential, following application of a tetanus. Long-term potentiation and LTD have received a great deal of attention as cellular models for learning and memory (Martin et al. 2000; Malenka and Bear 2004; Citri and Malenka 2008; Collingridge et al. 2010). In the CA1 and subiculum, LTP and LTD are induced by the activation

of postsynaptic N-methyl-D-aspartate (NMDA) receptors (Bliss and Collingridge 1993; Malenka and Bear 2004; Citri and Malenka 2008; Howland and Wang 2008; Behr et al. 2009; Collingridge et al. 2010), although other pre- and postsynaptic mechanisms also contribute (Malenka and Bear 2004; Lisman and Raghavachari 2006; Behr et al. 2009; Kullmann 2012). One important mechanism for the expression of LTP and LTD involves trafficking of postsynaptic α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptors (Collingridge et al. 2004, 2010; Derkach et al. 2007; Kessels and Malinow 2009). Other forms of long-term hippocampal synaptic plasticity include primed burst potentiation, a low threshold form of synaptic potentiation (Diamond et al. 1988), and late developing or low-frequency induced potentiation (Habib and Dringenberg 2010). Differences have been noted in the effects of low frequency stimulation on synaptic responses in the CA1 and subiculum, particularly in vivo. In the adult rodent CA1 region, low frequency stimulation (1–3 Hz) often fails to induce LTD, as is commonly reported in slices from younger rodents (Xu et al. 1997; Fox et al. 2007; Wong et al. 2007). In contrast, low frequency stimulation of the CA1-subiculum pathway induces a late developing potentiation in the subiculum (Anderson et al. 2000; Huang and Kandel 2005; MacDougall and Howland 2013a;b) and, if paired with postsynaptic depolarization, a muscarinic-dependent form of LTD (Li et al. 2005). In the next two sections, the reported effects of acute stress on these forms of short- and long-term synaptic plasticity will be reviewed. Data related to long-term synaptic plasticity will be reviewed first as the effects of acute stress on these forms of plasticity have been studied more comprehensively.

11.4 Effects of Acute Stress on Long-Term Synaptic Plasticity in the CA1 and Subiculum

11.4.1 CA1 Region

The majority of the research regarding the effects of acute stress on long-term synaptic plasticity in the hippocampal CA1 region has been reviewed (Kim and Yoon 1998; Kim and Diamond 2002; Diamond et al. 2005, 2007; Howland and Wang 2008; Collingridge et al. 2010). The initial report showing that exposure to acute stress impaired LTP in the CA1 region of hippocampal slices was published in 1987 (Foy et al. 1987), a finding that has been consistently replicated using both in vitro and in vivo preparations (Shors and Thompson 1992; Kim et al. 1996; Xu et al. 1997; Kim et al. 2001; Yang et al. 2004; Li et al. 2008; Cazakoff and Howland 2010; MacDougall and Howland 2013a; for reviews see Kim and Diamond 2002; Howland and Wang 2008). Importantly, the regulation of LTP by acute stress differs along the septo-temporal axis of the CA1 region, with disruptions in LTP occurring in the dorsal CA1 region and a surprising facilitation of a voltage-gated calcium

channel-dependent form of LTP in the ventral hippocampus following acute stress (Maggio and Segal 2007) that coincides with an increase in PPF ratios (Maggio and Segal 2012). Primed burst potentiation, a low threshold form of synaptic potentiation, is also impaired in the dorsal CA1 region of rats following exposure to acute stress (Diamond et al. 1990), even under conditions when LTP is not impaired (Meseches et al. 1999). Acute stress has also been widely reported to facilitate the induction of LTD in the CA1 region (Xu et al. 1997; Xu et al. 1998; Wong et al. 2007; Li et al. 2008; Dong et al. 2013; for reviews see Diamond et al. 2005; Howland and Wang 2008; Collingridge et al. 2010). The alterations in dorsal hippocampal LTP and LTD depend on activation of GRs (Xu et al. 1998; Yang et al. 2004, 2005; Cazakoff and Howland 2010), NMDA receptors (Kim et al. 1996; Wang et al. 2006; Wong et al. 2007), and intracellular signalling cascades including the extracellular signal-regulated kinase/mitogen-activated protein kinase (Yang et al. 2004). Whether these changes reflect a form of meta-plasticity or occur independently has been the subject of debate (Kim and Yoon 1998; Kim and Diamond 2002; Howland and Wang 2008), although increased glutamate release may contribute to the changes in hippocampal LTP and LTD following acute stress (Yang et al. 2005; Wong et al. 2007; Howland and Wang 2008; Reagan et al. 2012).

11.4.2 Subiculum

In contrast to the extensive characterization of the changes in long-term patterns of synaptic plasticity in the CA1 region in response to stress, scarce research has been conducted regarding the subiculum. Three in vivo studies in anesthetized rats have shown that acute stress disrupts LTP in the dorsal subiculum of rats, two using an acute restraint procedure (MacDougall and Howland 2013a;b) and the other systemic administration of the bacterial endotoxin lipopolysaccharide (Commins et al. 2001). While the changes in synaptic plasticity were shown to depend on GRs, acute injection of corticosterone alone failed to significantly alter plasticity in the subiculum even though the levels of circulating corticosterone were similar in acutely stressed and corticosterone-injected rats (MacDougall and Howland 2013b). In the same manner, late developing potentiation induced by low-frequency stimulation of the CA1-subiculum pathway was impaired by acute stress, but not corticosterone, due to activation of GRs (MacDougall and Howland 2013b). Interestingly, as LTP in the CA1-dorsal subiculum pathway appears to involve a presynaptic component (Commins et al. 1998a; MacDougall and Howland 2013b), the mechanisms by which this disruption occurs may be distinct from those in the CA3-CA1 synapse where postsynaptic modifications involving postsynaptic AMPA receptor trafficking may be more important (Fox et al. 2007; Wong et al. 2007; Dong et al. 2013).

11.5 Effects of Acute Stress on Short-Term Synaptic Plasticity in the CA1 and Subiculum

11.5.1 CA1 Region

Table 11.1 summarizes the published findings regarding the effects of acute stress on PPF and includes details related to the exact methodological parameters used in the experiments. In the CA1 region, studies have used both in vitro and in vivo preparations. Two studies have tested the effects of acute stress on PPF in the CA1 region of hippocampal slices. One study that used a severe stressor combining restraint with inescapable tail shocks found a disruption in CA1 LTP with no effect on PPF ratios in hippocampal slices from Long Evans rats (Shors and Thompson 1992). A second study exposed Wistar rats to ten shocks in a novel chamber and reported decreased PPF ratios and facilitated LTD in the CA1 region of hippocampal slices (Gao et al. 2008). Using an in vivo preparation in anesthetized rats, Cazakoff and Howland observed that 30 min of exposure to an elevated platform disrupted both PPF and LTP in the CA1 region that could be blocked with a GR antagonist (RU38486) administered before the acute stress (Cazakoff and Howland 2010 ; see also MacDougall and Howland 2013a). In contrast to the results observed in the subiculum (see below), reduced PPF was observed both before and after the high frequency tetanus was administered to induce LTP (Cazakoff and Howland 2010).

Three additional studies have tested the effects of bath application of corticosterone on PPF in the dorsal CA1 region of hippocampal slices. Karst and colleagues observed a rapid disruption in PPF and enhanced frequency of miniature excitatory postsynaptic currents following 10 min of corticosterone (100 nM) perfusion that depended on MR activation (Karst et al. 2005) and likely presynaptic activation of the extracellular signal-regulated kinase 1/2 pathway (Olijslagers et al. 2008). No change in PPF is observed 1–4 h following corticosterone perfusion (100 nM for 20 min; Karst and Joels 2005). Perfusion of a higher dose of corticosterone (1 or 10 μM) for longer (3 h) impaired PPF and LTP in another study, an effect related to decreases in brain-derived neurotrophic factor (Zhou et al. 2000).

11.5.2 Subiculum

To our knowledge, three in vivo studies have examined the effects of acute stress on PPF in the CA1-subiculum pathway while no data exist from in vitro experiments (Table 11.1). In one study, exploration of a novel box failed to alter PPF in the CA1-subiculum pathway (Commins and O'Mara 2000) while a second study showed that administration of the bacterial endotoxin LPS 4 h prior to in vivo recordings impaired PPF prior to delivery of a tetanus (Commins et al. 2001). The third study demonstrated that acute restraint stress (30 min), but not corticosterone injections

Table 11.1 The effects of acute stress or corticosterone administration on prepulse facilitation (PPF) and long-term synaptic plasticity in the CA1 and subiculum of the dorsal hippocampus. The mechanism involved in the reduction of PPF is noted where data exist. See the text for further details.

Strain/ species	Stressor	E-phys protocol	PPF effect	Long-term effect	Reference
CA3/Schaffer collateral-CA1 pathway, in vitro					
LE/rat	Restraint and tail shocks (60 shocks in 60 min)	HPC slices; stratum radiatum/CA1 pathway; PPF @ 50, 75, 100, 200 ms	N/C PPF	↓ LTP	Shors and Thompson (1992)
Wistar/rat	Shocks in novel chamber (10 shocks in 10 min)	Coronal HPC slices; stratum radiatum/CA1 pathway; PPF @ 60 ms	↓ PPF	↑ LTD	Gao et al. (2008)
C57BL6/ mouse	Cort (100 nM, 10 min)	Transverse HPC slices; CA3/Schaffer collateral-CA1 pathway; PPF @ 100 ms	↓ PPF (MR)	no data	Karst et al. (2005)
C57BL6/ mouse	Cort (100 nM, 20 min)	Transverse HPC slices; CA3/Schaffer collateral-CA1 pathway; PPF @ 100 ms 1–4 h following Cort	N/C PPF	no data	Karst and Joels (2005)
SD/rat	Cort (1 or 10 μM, 3 h)	Transverse HPC slices; CA3/Schaffer collateral-CA1 pathway; PPF @ 100 ms immediately following	↓ PPF (BDNF)	↓ LTP	Zhou et al. (2000)
CA3/Schaffer collateral-CA1 pathway, in vivo					
SD/rat	Elevated platform (30 min)	Urethane anesthetized; CA3/Schaffer collateral-CA1 pathway; PPF @ 25, 50, 100, 200 ms	↓ PPF (GR)	↓ LTP	Cazakoff and Howland (2010)
CA1-subiculum pathway, in vivo					
SD/rat	Restraint (30 min)	Urethane anesthetized; CA1-SUB pathway; PPF @ 25, 50, 100, 200 ms	↓ PPF (GR)	↓ LTP/ LDP	MacDougall and Howland(2013b)
Wistar/rat	Exposure to a novel environment	Sodium pentobarbitone/ urethane anesthetized; CA1-SUB pathway; PPF @ 50, 100 ms	N/C PPF	↑ LTD	Commins and O'Mara (2000)
Wistar/rat	LPS (4 h prior to recordings)	Sodium pentobarbitone/ urethane anesthetized; CA1-SUB pathway; PPF @ 50, 100 ms	↓ PPF	↓ LTP	Commins et al. (2001)
SD/rat	Cort (3 mg/kg)	Urethane anesthetized; CA1-SUB pathway; PPF @ 25, 50, 100, 200 ms	N/C PPF	N/C LTP/ LDP	MacDougall and Howland(2013b)

BDNF brain derived neurotrophic factor, *Cort* corticosterone, *GR* glucocorticoid receptor, *HPC* hippocampus, *LDP* late developing potentiation, *LE* Long-Evans, *LTP* long-term potentiation, *LTD* long-term depression, *MR* mineralocorticoid receptor, *N/C* no change, *SD* Sprague Dawley

(3 mg/kg), disrupted PPF prior to delivery of a tetanus (MacDougall and Howland 2013b; see also MacDougall and Howland 2013a. In both studies that showed PPF disruptions following acute stress, LTP was also disrupted by the stressor (Commins et al. 2001; MacDougall and Howland 2013b). As previously mentioned, the induction of LTP in the CA1-subiculum pathway has been shown to reduce PPF ratios (Commins et al. 1998; MacDougall and Howland 2013b), which may be indicative of a presynaptic locus for the mechanism(s) underlying LTP in this pathway (Commins et al. 1998; Behr et al. 2009). Importantly, acute stress was also shown to disrupt this reduction in PPF observed following administration of a tetanus, suggesting that acute stress may have effects on distinct forms of LTP observed in the CA1 and subiculum (MacDougall and Howland 2013b). Injections of the GR antagonist RU38486 prior to the stressor blocked the effects of acute stress both before and after administration of the tetanus (MacDougall and Howland 2013b).

11.6 Integration of the Effect of Acute Stress on Short- and Long-Term Forms of Synaptic Plasticity

Inspection of Table 11.1 reveals a complex set of findings related to short- and long-term synaptic plasticity in the CA1 and subiculum following acute stress or corticosterone treatment. Alterations in PPF are observed in six of the nine studies; however, the role of MRs and GRs in mediating the changes in PPF differed among the studies. One factor that likely contributed to these differences is the delay between the stressor/corticosterone treatment and electrophysiological measurements as the effects of acute stress on cognition and related brain circuits are well-known to be time dependent (de Quervain et al. 1998; Joels et al. 2006, 2012). Differences related to the timing of the stressor relative to the recordings in the studies can be illustrated by considering the demonstrated role of MRs in causing the reduced PPF following acute stress/corticosterone administration in some studies (Karst et al. 2005) versus GRs in others (Cazakoff and Howland 2010; MacDougall and Howland 2013b). Karst and colleagues used hippocampal slices and bath applied corticosterone for 10 min before measuring PPF (Karst et al. 2005). Under these conditions, the disrupted CA1 PPF depended on MR activation. Given the short time period for the MR-dependent reductions in PPF to be observed, these researchers proposed that a non-genomic effect of MR activation must be involved (Karst et al. 2005). In contrast, evidence that GR activation is necessary for the PPF disruptions in the CA1 and subiculum by acute stress was gained using in vivo recordings (Cazakoff and Howland 2010; MacDougall and Howland 2013b). In these experiments, the animals were exposed to acute stress for 30 min before being anesthetized. Once anesthetized, 60–90 min were needed to prepare the animal for recordings and lower the electrodes. Thus, the PPF measurements would have been taken 90–120 min after the HPA axis was activated and corticosterone was initially released in the response to the stressor. Previous studies suggest that GR activation significantly affects gene expression within a time frame of 1–3 h (Zhou et al. 2000;

Morsink et al. 2006, 2007). Thus, PPF may be altered over a broad timescale after acute stress: initially by the rapid non-genomic actions of MR activation and subsequently by the slower genomic changes following GR activation.

Glucocorticoid receptor-dependent disruptions of PPF following acute stress have also been reported for the perforant path to dentate gyrus pathway in vivo (Avital et al. 2006; although see also Bramham et al. 1998; Spyrka et al. 2011) and the medial prefrontal cortex in vitro (Musazzi et al. 2010; Popoli et al. 2012) in rats. Similarly to the studies described above that also noted a GR-dependent reduction in PPF (Cazakoff and Howland 2010; MacDougall and Howland 2013b), the electrophysiological recordings would have been performed hours after the stressor. Taken together, these findings indicate that while corticosterone has extremely rapid effects on PPF in the CA1 region (i.e., in minutes) that are caused by non-genomic actions of MRs (Karst et al. 2005), periods of acute stress recruit a GR-dependent change in PPF in a number of areas, including the CA1 and subiculum (Avital et al. 2006; Cazakoff and Howland 2010; Musazzi et al. 2010; MacDougall and Howland 2013b).

Similar timeframes for MR and GR-dependent effects of corticosterone have been noted in a study testing the effect of corticosterone on AMPA receptor trafficking using quantum-dot imaging, a technique which allows the diffusion of receptors to be quantified (Groc et al. 2008; Krugers et al. 2010). A rapid (<10 min), MR-dependent increase in membrane surface diffusion of GluA2 subunit-containing AMPA receptors was observed following application of corticosterone. Importantly, this effect likely depended on membrane bound MRs as a membrane impermeable BSA-corticosterone conjugate also produced the effect. In additional experiments, a slower (150 min) GR-dependent increase in GluA2-subunit containing surface expression was observed following corticosterone exposure (Groc et al. 2008; see also Martin et al. 2009).

Other differences among the studies summarized in Table 11.1 may explain why altered PPF following acute stress/corticosterone was reported in some (Zhou et al. 2000; Commins et al. 2001; Karst et al. 2005; Gao et al. 2008; Cazakoff and Howland 2010; MacDougall and Howland 2013b; Maggio and Segal 2012) but not others (Shors and Thompson 1992; Commins and O'Mara 2000; Karst and Joels 2005). While it is tempting to speculate that differences in the species/strain of rodents or in vitro/in vivo preparation used may contribute, the effects of acute stress on long-term synaptic plasticity are generally resistant to these factors. Secondly, the effects of corticosterone generally follow an inverted U-shaped relationship (Lupien and McEwen 1997; Park et al. 2006; Diamond et al. 2007) so the differences in doses of corticosterone must be taken into account. For example, application of high doses of corticosterone (1–10 μM) for multiple hours reduced CA1 PPF and LTP in hippocampal slices (Zhou et al. 2000) whereas application of 100 nM of corticosterone for 20 min had no effect on PPF assessed 1–4 h later (Karst and Joels 2005). Different effects of "acute stress" versus "elevations in corticosterone" have been noted in both electrophysiological and behavioural experiments related to the hippocampus (Kim et al. 2001, 2005; Kim and Diamond 2002; Woodson et al. 2003; MacDougall and Howland 2013b). Thus, elevations in corticosterone may be necessary, but not

sufficient, to alter synaptic plasticity. The transmission of emotional information regarding the stressor by the amygdala may be an additional critical factor necessary for acute stress to affect synaptic plasticity and cognition (Kim et al. 2001, 2005; Kim and Diamond 2002; Schwabe et al. 2012).

It is not surprising that acute stress has effects on short- and long-term patterns of synaptic plasticity given the established effects of acute stress on presynaptic and postsynaptic aspects of the glutamate signalling in the hippocampus and other areas including the prefrontal cortex (Popoli et al. 2012; Sanacora et al. 2012). One remaining issue relates to whether the effects of acute stress on short-term plasticity are due to the same or distinct mechanisms from those that cause the effects of acute stress on long-term synaptic plasticity. If the mechanisms are distinct, the possibility exists that alterations in short- and long-term synaptic plasticity following acute stress may underlie different effects of acute stress on cognition. Table 11.1 summarizes the findings related to long-term plasticity from the studies that also observed changes in PPF following acute stress in an effort to address this issue. In every study where both short and long-term synaptic plasticity were measured and PPF was impaired, long-term plasticity was also altered. Reduced PPF correlated with reduced LTP in four of the studies (Zhou et al. 2000; Commins et al. 2001; Cazakoff and Howland 2010; MacDougall and Howland 2013b) and increased LTD in one of the studies (Gao et al. 2008). In two of the studies, long-term plasticity was altered by acute stress while PPF was unaffected (Shors and Thompson 1992; Commins and O'Mara 2000). In two of the studies, a GR antagonist blocked the effects of acute stress on both PPF and long-term synaptic plasticity in the CA1 (Cazakoff and Howland 2010) and subiculum (MacDougall and Howland 2013b). Thus, these data suggest that the alteration in short- and long-term forms of synaptic plasticity is initiated by activation of GRs. Whether the signalling pathways downstream of GRs mediating these effects on short- and long-term plasticity are the same or different remains an open question.

11.7 Linking the Effects of Acute Stress on Synaptic Plasticity in CA1 and Subiculum to Hippocampal-Dependent Behaviour

The effects of acute stress on cognition are complex and influenced by a variety of factors including the type of cognition examined, specifics of the stressor, timing of the stressor, level of intrinsic arousal associated with the task, and characteristics of the subject examined (Kim and Diamond 2002; Joels et al. 2006; Shors 2006; Diamond et al. 2007; Sandi and Pinelo-Nava 2007; Holmes and Wellman 2009; Cazakoff et al. 2010; Schwabe et al. 2012). The focus of the following discussion will be effects of acute, extrinsic stress (i.e., stress not directly associated with the task) on spatial and recognition memory in rodents. In most cases, extrinsic stress disrupts hippocampal-dependent spatial learning and memory (for review, see Cazakoff et al. 2010), effects that are hypothesized to be caused by alterations in long-term

synaptic plasticity caused by acute stress (Kim and Diamond 2002; Diamond et al. 2005, 2007; Wong et al. 2007; Howland and Wang 2008; Cazakoff et al. 2010). Importantly, both the dorsal CA1 and subiculum are both involved in processing spatial information and memory (Morris et al. 1990; McNaughton et al. 1996; O'Mara et al. 2009); however, their anatomical positions and behavioural data (Deadwyler and Hampson 2004) suggest that their roles are likely distinct (Behr et al. 2009). While the dorsal CA1 receives strong input via the glutamatergic Schaffer collaterals from CA3 and inputs from the cortex via the temporoammonic pathway (Behr et al. 2009), the subiculum receives strong projections from the CA1 (Amaral et al. 1991) and cortical areas including the entorhinal, perirhinal, and postrhinal areas (Naber et al. 2001; Behr et al. 2009; O'Mara et al. 2009). Thus, the subiculum is in a privileged position to receive both highly processed information that has made its way through the hippocampus and "raw" sensory information directly from the cortex (Behr et al. 2009). As reviewed above, acute stress disrupts short- and long-term patterns of synaptic plasticity in both the CA1 and subiculum. These studies have examined the traditional pathways of information flow through the hippocampal system, the CA3-CA1 pathway and the CA1-subiculum pathway. Given the role of both regions in spatial memory formation, it is reasonable to conclude that the impairments in synaptic plasticity in both regions of the circuit contribute to the deficits in spatial memory retrieval observed following acute stress (O'Mara 2006; Cazakoff et al. 2010; MacDougall and Howland 2013b). One interesting test of this hypothesis would be to assess whether the pharmacological agents reported to block the effects of acute stress on CA1 synaptic plasticity and spatial memory retrieval (Howland and Wang 2008; Cazakoff et al. 2010) also block the effects of acute stress on synaptic plasticity in the subiculum. Two examples of such agents are the GluN2B subunit-selective NMDA receptor antagonist Ro25–6981 (Wang et al. 2006; Wong et al. 2007; Howland and Cazakoff 2010) and transient receptor potential vanilloid 1 agonist capsaicin (Li et al. 2008).

The role of corticosteroid receptors in the effects of acute stress on hippocampal-mediated behaviour is also of interest given their roles in the acute stress effects on synaptic plasticity. Interestingly, convergence between the time-dependent involvement of MRs and GRs in the alterations of synaptic plasticity and spatial learning and memory by acute stress has been gained from recent studies (Dorey et al. 2011; Dorey et al. 2012). The studies used a delayed alternation procedure on a T maze that involved forcing mice to enter one arm of the maze twice during a training period. In a test session 24 h later, mice were allowed to enter either the arm they had visited during training or the opposite "novel" arm. Control mice displayed robust preference for entering the arm they had not entered during training. Exposure to acute stress 15 min before the test trial disrupted alternation behaviour, an effect that was mimicked by injecting the mice with membrane impermeable corticosterone injections suggesting that a membrane bound corticosteroid receptor was involved in the effect (Dorey et al. 2011). Intra-hippocampal microinfusions of an MR, but not a GR, antagonist before acute stress or corticosterone injections block their effects on delayed alternation. In a subsequent study, the same researchers showed that blockade of MRs in the dorsal hippocampus prevented the stress induced dis-

ruptions in delayed alternation at short (15 min), but not long (60–105 min), delays. Blocking GRs prevented the memory deficit at 60 min (dorsal hippocampus) and 105 min (ventral hippocampus), but not the short (15 min) delay (Dorey et al. 2012). In another study, the disruptive effects of corticosterone administration on spatial memory retrieval in a water maze task were also reversed by an MR antagonist, but not a GR antagonist or protein synthesis inhibitor, suggesting a non-genomic action of MRs in mediating the effect of corticosterone or acute stress on spatial memory retrieval (Khaksari et al. 2007). These behavioural data may appear to conflict with the studies reviewed showing that the effects of acute stress on synaptic plasticity in the CA1 and subiculum depend on GR activation (Xu et al. 1998; Cazakoff and Howland 2010; MacDougall and Howland 2013b); however, two points are worth emphasizing in this regard: (1) To our knowledge, no published data are available assessing the effects of MR antagonists on the alterations in hippocampal synaptic plasticity caused by acute stress in a time frame of minutes and (2) the time frame after stress assessed in the studies on synaptic plasticity is consistent with the effects of GR antagonists on stress-induced memory disruptions (i.e., 60 min or longer; Dorey et al. 2012). Thus, one critical experiment will be to assess the potential time-dependent effects of MR and GR antagonists on the alterations in synaptic plasticity caused by acute stress. Because the time required for preparing the animals for recordings in brain slices or under anaesthesia is too long to assess the potential effects of MR antagonists on the alterations of synaptic plasticity caused by acute stress, field potential recordings in freely moving rodents will be necessary.

Recognition memory is routinely assessed for a variety of stimuli including objects and spatial locations in different paradigms (Dere et al. 2007; Winters et al. 2008). While the neural substrates mediating recognition memory remain controversial, roles for the perirhinal cortex in object recognition and hippocampus in spatial recognition tasks are supported by the literature (Dere et al. 2007; Howland et al. 2008; Winters et al. 2008). Recordings of local field potentials from the CA1 and subiculum during an object recognition task showed increased theta power in the subiculum, but not CA1 region, during object recognition (Chang and Huerta 2012), which is interesting in light of the direct input the subiculum receives from perirhinal cortex (Behr et al. 2009; O'Mara et al. 2009). Object recognition and object-place recognition are both susceptible to disruption by acute stress (Baker and Kim 2002; Cazakoff et al. 2010; Howland and Cazakoff 2010; Li et al. 2012); however, the potential role of alterations in synaptic plasticity by acute stress in mediating these effects has received scant attention. The mechanisms in perirhinal cortex that support object recognition memory are distinct from those typically ascribed to spatial memory in the hippocampus. Long-term depression caused by AMPA receptor endocytosis in perirhinal cortex is implicated in object recognition memory under normal conditions (Griffiths et al. 2008; Cazakoff and Howland 2011) whereas AMPA receptor endocytosis in the CA1 region has been reported to mediate the effects of acute stress on memory retrieval (Wong et al. 2007). The disruptive effects of acute stress on both spatial memory retrieval and object recognition can be blocked by systemic injections of the GluN2B subunit-selective NMDA receptor antagonist Ro25–6981 (Howland and Cazakoff 2010). Future studies examining the

effects of acute stress on synaptic plasticity in the reciprocal pathway connecting the subiculum to perirhinal cortex will be critical for fully appreciating the potential role of alterations in synaptic plasticity in mediating the effects of acute stress on recognition memory.

11.8 Conclusion

Periods of acute stress have significant effects on different types of synaptic plasticity in the dorsal hippocampus. This chapter reviewed evidence that acute stress alters short-term synaptic plasticity by impairing PPF ratios in both the CA1 and subiculum. The mechanisms mediating these effects appear to involve release of the hormone corticosterone acting at its two main receptors in a time-dependent manner. Rapid disruptions in PPF in the minutes following corticosterone application are caused by activation of MRs, likely signalling through a non-genomic pathway. Disruption of PPF later in time (in hours after the stressor) appears to involve GR activation. The effects of acute stress on long-term synaptic plasticity in both the CA1 and subiculum should be taken into account when developing theories regarding the neural circuitry underlying the effects of acute stress on hippocampal-dependent tasks.

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