Chapter 9
Neural-Cognitive Effects of Stress in the Hippocampus

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Abstract It is now well-accepted that uncontrollable (i.e., acute traumatic, prolonged) stress can have lingering effects on the hippocampus. At the behavioral level, evidence from human and animal studies indicates that stress generally impedes performance in a variety of hippocampal-dependent memory tasks. At the neural level, animal studies have shown that stress impairs induction of long-term potentiation (LTP), a form of synaptic plasticity, in the hippocampus. Because the hippocampus is important for certain forms of long-term memory and because LTP has properties desirable of an information storage mechanism, it has been hypothesized that stress-induced alterations in hippocampal plasticity contribute to decreased memory functioning following stress exposure. This chapter reviews the effects of stress on three vertically related levels of hippocampal functions—synaptic plasticity, neural activity and memory—and the recent evidence implicating the amygdala as a crucial component of the central stress mechanism.

Abbreviations

ACTH	Adrenocorticotropic hormone
AMYG	Amygdala
APV	DL-2-amino-5-phosphonovaleric acid
CORT	Cortisol/corticosterone
CRF	Corticotropin-releasing factor
GABA	Gamma-aminobutyric acid
GR	Glucocorticoid receptor
HPA-axis	Hypothalamic-pituitary-adrenal axis
I/O	Input/output
LTD	Long-term depression
LTP	Long-term potentiation
mPFC	Medial prefrontal cortex
MR	Mineralocorticoid receptor
NMDA	*N*-methyl-D-aspartate

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PTSD	Post-traumatic stress disorder
S	Stimulus
R	Response

9.1 Introduction

Stress is a biologically significant factor that plays pervasive roles in our lives, from influencing daily behaviors to precipitating symptoms of mental health disorders. Hence, stress presents a natural means to investigate the socio-environmental contributions to various psychopathologies, such as anxiety, panic and posttraumatic stress disorders (PTSD), depression, schizophrenia, and relapse in drug use (Kim and Diamond 2002; Lupien et al. 2009; Sinha et al. 2011).

Semantically, stress describes any significant socio-environmental conditions that require appropriate physiological and/or behavioral readjustment (or adaptation) that serves to preserve the well-being of the organism (Selye 1956, 1973; McEwen and Sapolsky 1995). At present, stress phenomena are conceptually and procedurally dichotomized as physical (real) versus psychological (perceived), early life versus adulthood, and acute versus chronic (e.g., Foy et al. 2005; Kosten et al. 2012). While *stress* refers to an unpleasant state (distress) in colloquial speech, a related concept, *eustress,* has been proposed to represent positive valence of stress (e.g., voluntary exercise), highlighting the conceptual distinction between the emotional perception of stress and the fundamental process underlying physiological and behavioral adaptation (Selye 1974).

A number of putative stress paradigms are utilized in different laboratories, making it sometimes difficult to evaluate experimental findings across studies. To standardize the framework of stress that can be applied across different animal and human models, one proposal (Kim and Diamond 2002; Kim and Haller 2007) suggested that stress must satisfy three conditions: (1) heighten the excitability or arousal of the organism, (2) induce perceived aversiveness, and (3) decrease perceived controllability of the situation. This operational definition makes a clear distinction between stress and other aversive states such as fear. For instance, traffic congestions can elicit arousal, be aversive (but not fearful), and evoke a loss of controllability (if there is no alternative route) in most people, and in such case satisfy the three stipulations of stress. While the *stress response* is an adaptive mechanism, the prolonged stress response can have deleterious physiological and psychological outcomes, such as hypertension, diabetes, gastric-intestinal ulceration, depression, and anxiety disorders (Sapolsky 1992; Rosen and Schulkin 1998).

In recent decades, researchers have focused on the adverse effects of stress on brain-memory systems (Kim and Diamond 2002; Shors 2004). Because the effects of stress on memory are similar between humans and a number of animals, animal models provide a valuable means to investigate the neurocognitive effects of stress. At present, neurobiological studies have found that uncontrollable stress alters syn-

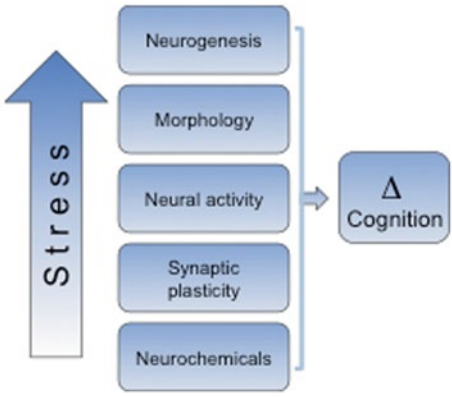

Fig. 9.1 Neurobiological effects of stress in the hippocampus. As the intensity and duration of stress increases, alterations in neurochemicals, synaptic plasticity, neural activity, morphology, and neurogenesis occur in the hippocampus. These changes can contribute to stress-induced dysfunctions in memory

aptic plasticity and neuronal morphology (soma size, dendritic arborization), exacerbates neurotoxicity and suppresses neurogenesis in the hippocampus (Fig. 9.1) (Kim and Yoon 1998). These stress-induced physiological changes, presumably, can influence ensuing learning and memory functions. Accordingly, stress presents a natural means to study the contribution of learning and memory dysfunction to various psychopathologies. While diverse stress paradigms have been shown to influence a number of brain-memory systems, this chapter will highlight the effects of acute, uncontrollable stress on hippocampal plasticity, neural activity and memory, and the role that the amygdala plays in the emergence of stress effects.

9.2 Stress Effects on Hippocampal Memory

Almost a half century ago, Seligman, Maier, and Overmier made the significant discovery that animals that had previously experienced uncontrollable stress (i.e., random, inescapable electric shocks) were impaired in learning to escape from footshocks in the shuttle box task, a phenomenon known as *learned helplessness* (Seligman and Maier 1967; Overmier and Seligman 1967). According to the learned helplessness hypothesis, when an organism learns that its behavior (response, R) and aversive outcomes (stimulus, S) are independent, this learning produces cognitive, emotional, and motivational transformations that later hinder learning of other tasks. In laboratory settings, humans, dogs, cats, rats, and even fish have been shown to demonstrate learned helplessness following exposure to uncontrollable stress (loud noise, electric shock). Importantly, when the cessation of an aversive S is made contingent upon the animals R (e.g., a rat emitting a wheel turn R to terminate a tailshock S), the learning of this S-R association (namely, controllability) protects the animal from developing learned helplessness (Maier and Seligman 1976). Subsequent studies have revealed that stress particularly interferes with behavioral tasks that depend on the hippocampus (Kim and Yoon 1998).

The hippocampus is a part of the medial temporal lobe system, which is crucial for the formation of long-term declarative (explicit) memory in humans (Scoville and Milner 1957; Eichenbaum 2000) and spatial (relational) memory in rodents (OKeefe and Nadel 1978; Morris et al. 1982, 1998). Declarative memory is generally defined as information about facts and events that can be consciously (or verbally) recollected. In animals, however, the human declarative-like memory can only be established by assessing whether hippocampal lesions abolish particular behaviors in learning tasks. The hippocampus is highly concentrated with receptors for corticosteroids-the principle glucocorticoids synthesized by the adrenal cortex (*cortisol* in human, *corticosterone* in rodent; CORT) to regulate general cellular energy metabolism processes-and participates in terminating the stress response through glucocorticoid-mediated negative feedback of the hypothalamic-pituitary-adrenal (HPA) axis (Axelrod and Reisine 1984). Because its secretion is highly responsive to stress, CORT is commonly referred to as the "stress hormone" (or even tacitly believed as a stress-producing hormone). In the rodent hippocampus, CORT has been found to alter the metabolic, physiologic, and genomic functions of neurons (Sapolsky 1992). As a result, the mnemonic functions of the hippocampus appear to be sensitive to stress.

Consistent with this view, a large body of evidence indicates that exposures to stress and/or stress hormones negatively impact hippocampal-dependent memory tasks in humans and animals (see Lupien and McEwen 1997). For example, PTSD patients exhibit deficits in verbal recall tasks when compared to control subjects (Bremner et al. 1993; Utto et al. 1993). Injections of CORT in healthy human subjects have been reported to selectively impair verbal declarative memory, sans affecting nonverbal (nonhippocampal) memory (Newcomer et al. 1994; Kirschbaum et al. 1996; de Quervain et al. 2000; Kuhlmann et al. 2005). Moreover, hypercortisolemia conditions in certain depressive patients and those afflicted with Cushings disease have been implicated in declarative memory impairments (Starkman et al. 1992; Sapolsky 2000). However, administration of CORT has also been reported to selectively enhance the long-term recall of emotionally arousing (but not neutral) pictures (e.g., Buchanan and Lovallo 2001), suggesting that stress hormone effects may be more subtle and complex than previously reported.

Similar to human studies, rats subjected to uncontrollable stress (or administered high doses of CORT) show memory deficits in various hippocampal-dependent behavioral tasks (e.g., Luine et al. 1993; de Quervain et al. 1998). The test par excellence of hippocampal memory in rodents is the spatial memory task, typically utilizing variations of Oltons 8-arm radial maze (Olton and Samuelson 1976) and Morris water maze (Morris 1981). In a series of elegant experiments, Diamond and colleagues have shown that stress impairs hippocampal-dependent spatial working memory while hippocampal-independent spatial reference memory is unaffected (Diamond and Rose 1994; Diamond et al. 1999; Woodson et al. 2003).

Spatial memory deficits have also been reported in transgenic mice with elevated CORT levels caused by the central over-expression of corticotropin-releasing factor (CRF) (Heinrichs et al. 1996). CRF, a neuropeptide secreted by the paraventricular nucleus of the hypothalamus, triggers the release of adrenocorticotropic hormone

(ACTH) from the pituitary gland, and ACTH in turn stimulates the production and secretion of glucocorticoids by the adrenal gland (Sapolsky 1992). Paralleling the spatial memory deficits are recent findings that stress impairs the stability of place cell firing rates (Kim et al. 2007; Passecker et al. 2011). Hippocampal place cells are thought to support spatial learning and navigation by encoding memories of familiar spatial locations (O'Keefe and Distrovsky 1971; OKeefe and Nadel 1978).

The stress effects on hippocampal memory do not seem to be limited to spatial information in rodents. Other studies found that stress also impairs nonspatial (hippocampal-dependent) object recognition memory (Beck and Luine 1999; Baker and Kim 2002). Stress also disrupts medial prefrontal cortex (mPFC)-based spatial working memory on a T-maze task (Arnsten and Goldman-Rakic 1998; Qin et al. 2009) as well as decision-making in a foraging task in rats (Graham et al. 2010).

Interestingly, the same stress that impairs hippocampal memory has been found to enhance the relative use of competing hippocampal-independent memory (e.g., the caudate-dependent response memory) in rats and humans (Kim et al. 2001; Pruessner et al 2008; Wingard and Packard 2008; Quirarte et al. 2009; Lovallo 2010; Schwabe et al. 2007; Schwabe and Wolf 2012). Stress has also been shown to enhance aversive memory, such as fear and eyeblink conditioning (Beylin and Shors 2003; Conrad et al. 1999a; Jackson et al. 2006; Rau et al. 2005). It remains to be determined, however, whether the learning enhancements in other behavioral tasks are due to direct effects of stress on those brain-memory systems or due to indirect effects of stress reducing the hippocampus ability to compete with other brain-memory systems. Thus, although the study of individual memory systems affected by stress has proved to be useful, particularly in the hippocampus, recent data increasingly point towards complex interactions between stress and multiple brain-memory systems (Kim and Baxter 2001).

9.3 Stress Effects on Hippocampal Synaptic Plasticity

Long-term potentiation (LTP) is characterized by an enduring increase in synaptic transmission resulting from high frequency stimulation (or tetanus) of afferent fibers (Bliss and Lomo 1973; Bliss and Gardner-Medwin 1973). Because LTP occurs rapidly, is stable over time, requires cooperativity (i.e., adequate afferents to reach threshold), is strengthened by repetition, and demonstrates input specificity and associativity, LTP has long been proposed as a synaptic model of information storage in the mammalian brain (Bliss and Collingridge 1993; Martin et al. 2000). In 1987, Thompson and colleagues found that hippocampal slices prepared from rats that received 30 min of intermittent tailshocks while being restrained exhibited striking deficits in the Schaffer collateral/commissural-cornu Ammonis 1 (CA1) LTP (Foy et al. 1987). Importantly, hippocampal slices taken from rats that were able to terminate the shock showed relatively normal LTP, while slices from "yoked" animals that received the identical shock schedule without control exhibited severely impaired LTP (Shors et al. 1989). Hence, similar to learned helplessness, the LTP

impairment appears to be largely due to the psychological, rather than physical, qualities of stress. Other forms of psychological stress, such as forced exposures to a novel chamber or to a predator, have also been found to impede LTP and/or primed-burst potentiation (a low threshold form of LTP) in behaving rats (Diamond et al. 1990; Xu et al. 1997; Diamond and Park 2000).

Stress-induced LTP impairments have also been observed in other regions of the hippocampus (Shors and Dryver 1994), and following 30-min restraint + shock stress, LTP deficits continue up to 48 h in rats (Shors et al. 1997) and 24 h in mice (Garcia et al. 1997). There seems to be a critical stress threshold for LTP impairment as 10-min restraint + shock stress, while producing robust fear conditioning and elevating corticosterone levels, does not impair LTP (Shors et al. 1989). Other studies indicate a time-dependent, biphasic effect on hippocampal LTP (an enhancing effect on LTP followed by a longer-lasting suppressing effect on LTP) (Akirav and Richter-Levin 1999), and stress has been reported to enhance theta-burst stimulation-induced LTP but impair high-frequency stimulation-induced LTP in the mouse hippocampus (Blank et al. 2002). These findings suggest that differences in stress paradigms, in vitro versus in vivo recordings, tetanus patterns, and species must be considered when evaluating stress effects on hippocampal synaptic plasticity.

The discovery that stress impairs hippocampal LTP is significant because it offers a testable synaptic mechanism to investigate stress-induced memory deficits, and because the LTP impairment can serve as a "neurophysiological marker" to compare behavioral consequences associated with different stress paradigms. For example, not all putative stress procedures would be expected to impair LTP and/or memory. Regardless, the relationship between stress effects on LTP and memory in the hippocampus is consistent with the hypothesis, namely Hebbs (1949) postulate, that memories are stored via changes in the pattern of synaptic connections.

In theory, LTP alone cannot provide a dynamic synaptic model for information storage; decreases in synaptic efficacy are essential to normalize synaptic strength and prevent LTP saturation (Sejnowski 1977). This is accounted for by long-term depression (LTD) characterized by a decrease in synaptic efficacy following low-frequency stimulation of afferent fiber which, like LTP, has several properties desirable for an information storage mechanism (e.g., longevity and input specificity) (Bear and Malenka 1994; Dudek and Bear 1992). When stress effects were examined in the Schaffer collateral/commissural-CA1 pathway, the same stress that impaired LTP was found to enhance LTD (Kim et al. 1996; Xu et al. 1997). Moreover, administration of a competitive *N*-methyl-D-aspartate (NMDA) receptor antagonist prior to stress blocked stress effects on both LTP and LTD (Table 9.1). These findings indicate that stress effects on LTP and LTD are related (see also Coussens et al. 1997; Diamond et al. 2004).

Two possibilities can explain the opposing effects of stress on LTP and LTD (Fig. 9.2). Since LTP is known to be "saturable" (i.e., has an upper limit of potentiation), if LTP or LTP-like changes occur in the hippocampus during stress, then any following LTP will be occluded due to a ceiling-like effect, whereas LTD can now be enhanced because the range for synaptic depression has increased (e.g., Kim et al. 1996; Diamond et al. 2004). This possibility is analogous to learned helpless-

Table 9.1 A summary of stress effects on in vitro LTP and LTD

Hippocampus (CA1)[a]	LTP	LTD
Control (unstressed)	+	−
Stressed	−	+
Control + APV	−	NA
Stressed + APV	NA	−
Control (from LTP state)	NA	−
Control (from LTP state) + APV	NA	+
Stressed (from LTD state)	+	NA
Stressed (from LTD state) + APV	−	NA
Stressed with NMDA antagonist	+	−

+ present or enabled, − absent or attenuated, *NA* not applicable, *LTP* long-term potentiation, *LTD* long-term depression, *APV* DL-2-amino-5-phosphonovaleric acid, *NMDA* N-methyl-D-aspartate
[a] Slices prepared from adult male rats. Modified from Kim et al. 1996

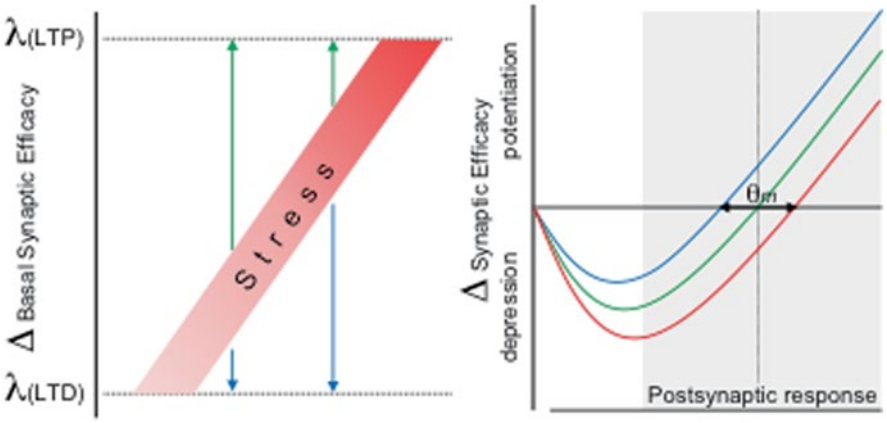

Fig. 9.2 Hypothetical models to account for stress effects on hippocampal synaptic plasticity. *Left*: The saturation hypothesis posits that stress produces long-term potentiation (*LTP*)-like changes in hippocampal synapses which then occlude subsequent LTP but enhance long-term depression (*LTD*) (λ, limit of plasticity). *Right*: The metaplasticity hypothesis proposes that stress shifts the modification threshold, θm, to the right (*represented by the red line*) so that ensuing synaptic changes favor LTD over LTP. (Adapted from Kim and Yoon 1998)

ness, wherein the animals learning of the independence between its behavior and the aversive situation interferes with subsequent memory functioning. A different possibility is that stress produces a "metaplastic" effect (i.e., higher-order plasticity that influences ensuing plasticity) in the hippocampus such that the threshold for LTP and LTD is biased towards LTD over LTP induction (see Abraham and Tate 1997; Kim and Yoon 1998). In order to reveal whether saturation or metaplasticity underlies stress effects on hippocampal plasticity, future studies will need to methodically monitor the input/output (I/O) functions in the hippocampus (e.g., the Schaffer collateral/commissural-CA1 pathway) while the animal transitions from

the baseline to during stress to post-stress. If uncontrollable stress produces LTP-like changes, then there should be differences in the baseline synaptic transmission when I/O functions are compared between baseline versus during and after stress. Specifically, the I/O functions should increase during the stress and such change should remain stable after stress. If stress produces metaplastic changes instead, then there should be no differences in I/O functions between baseline versus during and after stress.

9.4 Glucocorticoids and Hippocampal Plasticity

Contemporary stress research has consistently implicated corticosteroids (and other neurochemicals of the HPA-axis) as the main causes of stress effects on the hippocampus (McEwen and Gianaros 2011; Popoli et al. 2012; Ulrich-Lai and Herman 2009; Joels and Baram 2009). The hippocampus is enriched with both the high-affinity *Type-I* mineralocorticoid receptors (MR) and the lower-affinity *Type-II* glucocorticoid receptors (GR) (Reul and de Kloet 1985), and CORT actions through these receptors have been reported to mimic stress effects on hippocampal plasticity.

A dual relationship between the level of CORT and the magnitude of LTP has been described, where both low (via adrenalectomy) and high (via administration) levels of CORT are associated with impaired LTP (Diamond et al. 1992). Other studies have showed that selective activation of MRs increases LTP while added activation of GRs attenuates LTP and enhances LTD (e.g., Pavlides et al. 1995). This suggests that basal (low) levels of CORT enhance LTP through preferential stimulation of the high-affinity MRs and, during stress, GR stimulation turns out to be important because levels of CORT become high enough to saturate low-affinity receptors (McEwen and Sapolsky 1995). Behavioral studies found similar results-spatial memory is impaired with GR but not MR activation (Vaher et al. 1994; Conrad et al. 1999b; Oitzl et al. 2001). Bath application of CORT also prolongs calcium-dependent afterhyperpolarization of CA1 neurons (Kerr et al. 1989; Nair et al. 1998), which would decrease cell excitability and in so doing affect synaptic plasticity.

If corticosteroids are the main contributing factors in the mediation of stress effects, then removing them during stress and directly applying them in absence of behavioral stress, should preclude and produce stress effects, respectively. However, there are behavioral, synaptic plasticity and neural activity data from animal studies inconsistent with this simple linear neurochemical-level stress effect notion (Shors et al. 1989, 1990; Foy et al. 1990; Woodson et al. 2003; Stranahan et al. 2006). Very recent studies have reported that both stress and environmental enrichment significantly and comparably elevate CORT levels but have opposite effects on hippocampal neurogenesis (e.g., Schoenfeld and Gould 2012); findings that are incompatible to those in vivo and in vitro studies where CORT administration mimics behavioral stress effects. It is important to recognize that, like CORT, other hormones, peptides, and neurotransmitters implicated in stress (such as CRF, sero-

tonin, dopamine, enkephalins) also have multifold functions and none are known to respond uniquely to stress, and thus none of them is likely to be a sufficient mediator of stress effects.

9.5 Amygdala and Stress Effects on Hippocampus

Emerging evidence indicates that the amygdala is crucial in mediating stress-related behaviors and modulating hippocampal function. The amygdala is one of the principal structures of the limbic system that has access to sensory inputs from various brain regions (such as the thalamus, the neocortex) and sends projections to autonomic and somatomotor structures involved in defensive responses (such as the bed nucleus of stria terminalis for activating stress hormones, the periaqueductal gray for defensive behavior, the lateral hypothalamus for sympathetic activation) (see LeDoux 1996). Such rich sensory-amygdala-defensive (autonomic and motor) connections can explain how amygdalar lesions can prevent stress-induced gastric erosions (Henke 1981), analgesia (Helmstetter 1992), and anxiety-like behaviors (Adamec et al. 1999).

McGaugh and colleagues (Packard et al. 1994; McGaugh 2000; Roozendaal et al. 2003) have shown that pharmacological manipulations that alter synaptic transmissions in the amygdala (such as GABA, opioid, norepinephrine, and acetylcholine) can modulate memory strength in the hippocampus. Other studies have reported that lesions, stimulations, and drug infusions in the amygdala can also regulate LTP magnitude in the dentate gyrus (Abe 2001; Akirav and Richter-Levin 1999, 2002). Hence, the amygdala, via its (largely ipsilateral) projections to the hippocampus (Krettek and Price 1977; Pikkarainen et al. 1999), might also regulate stress effects on the hippocampus.

Consistent with this notion, amygdalar lesions have been found to block stress effects on hippocampal LTP and spatial memory in rats (Kim et al. 2001). Similarly, temporary inactivation of the amygdala via the $GABA_A$ receptor agonist muscimolprior to stress effectively blocked stress-induced physiological and behavioral effects (Kim et al. 2005). Intra-amygdalar muscimol also blocked spatial memory impairment following predator stress experience (Park et al. 2008). Because immediate post-stress muscimol infusions into the amygdala failed to prevent stress effects on LTP and memory, the critical time window of amygdalar activity is during (and not after) stress (Kim et al. 2005). It should be mentioned that amygdalar lesions/inactivation blocked stress effects on hippocampal LTP and memory despite the increase in corticosterone secretion to stress (Kim et al. 2001, 2005). An earlier study implicated the NMDA receptors in the amygdala in mediating stress-induced facilitation of classical eyeblink conditioning (Shors and Mathew 1998). Thus, it is likely that NMDA receptor-dependent plasticity in the amygdala is somehow involved in mediating stress effects on hippocampal plasticity and memory (Kim et al. 1996). Recently, electrical stimulation of the amygdala was found to selectively suppress CA1 LTP in the hippocampus (Vouimba and Richter-Levin 2005)

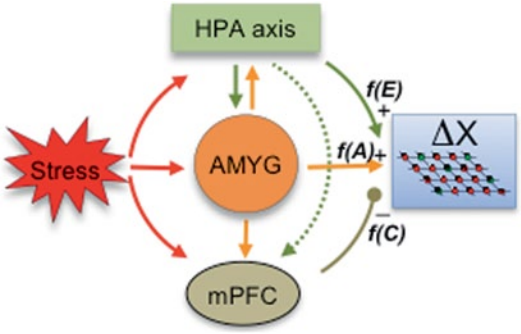

Fig. 9.3 A connectionist model of stress. The hypothalamic-pituitary-adrenal axis (*HPA*) axis (signifying the function of excitability, *f*(*E*)), amygdala (*AMYG*; aversiveness, *f*(*0*)), and medial prefrontal cortex (*mPFC*) (controllability, *f*(*C*)) interact to produce alterations (ΔX) in stress-vulnerable structures (e.g., the hippocampus). The model posits that HPA and AMYG exert excitatory (+) stress influences while mPFC exerts inhibitory (−) stress influence. (Adapted from Kim and Diamond 2002)

and produce stress-like impairment effects on hippocampal place cells (Kim et al. 2012). These findings suggest that the amygdala is a critical component of the central stress mechanism that alters hippocampal functioning (Fig. 9.3).

Stress has also been found to induce LTP and morphological changes in the amygdala. Unlike the hippocampus, which inhibits stress-induced HPA activation, the amygdala enhances glucocorticoid secretion in response to stress (Herman et al. 2005). Moreover, in contrast to hippocampal effects, stress (i.e., chronic immobilization stress) enhances LTP and increases growth of dendrites and spines in amygdalar neurons (Vyas et al. 2002, 2003; Mitra et al. 2005; Radley and Morrison 2005). These changes in the amygdala have been proposed to underlie stress-induced symptoms of chronic anxiety disorders (McEwen 2004). However, because different stress paradigms were used in hippocampal and amygdalar studies, it remains to be investigated whether neurophysiological changes in the amygdala precede and/or are prerequisite to stress-induced changes in the hippocampus. Thus, additional work is necessary to understand the nature of amygdala–hippocampal interaction during stress.

9.6 Summary

Contemporary stress research has focused on the effects of particular hormones (e.g., glucocorticoids), peptides (e.g., CRF, enkephalins), or neurotransmitters (e.g., serotonin, dopamine) on intracellular signaling cascades, synaptic plasticity, structural changes, cell death, and neurogenesis, which has generated a wealth of information. However, given that these chemical messengers are also engaged in

nonstress functions, it is likely that focusing on specific chemical messengers cannot provide an adequate representation of how uncontrollable stress impacts brain and behavior. Recent data from stress-amygdala-mPFC studies increasingly point towards complex neural-endocrine interactions in mediating stress effects on the hippocampus. Thus, consideration of multiple stress factors and their dynamics will advance our current understanding of the neural-cognitive effects of stress that may lead to stress-related psychopathology.

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