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Tuning synaptic transmission in the hippocampus by stress: the CRH system

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To enhance survival, an organism needs to remember—and learn from—threatening or stressful events. This fact necessitates the presence of mechanisms by which stress can influence synaptic transmission in brain regions, such as hippocampus, that subserve learning and memory. A major focus of this series of monographs is on the role and actions of adrenal-derived hormones, corticosteroids, and of brain-derived neurotransmitters, on synaptic function in the stressed hippocampus. Here we focus on the contribution of hippocampus-intrinsic, stress-activated CRH-CRH receptor signaling to the function and structure of hippocampal synapses. Corticotropin-releasing hormone (CRH) is expressed in interneurons of adult hippocampus, and is released from axon terminals during stress. The peptide exerts time- and dose-dependent effects on learning and memory via modulation of synaptic function and plasticity. Whereas physiological levels of CRH, acting over seconds to minutes, augment memory processes, exposure to presumed severe-stress levels of the peptide results in spine retraction and loss of synapses over more protracted time-frames. Loss of dendritic spines (and hence of synapses) takes place through actin cytoskeleton collapse downstream of $CRHR_1$ receptors that reside within excitatory synapses on spine heads. Chronic exposure to stress levels of CRH may promote dying-back (atrophy) of spine-carrying dendrites. Thus, the acute effects of CRH may contribute to stress-induced adaptive mechanisms, whereas chronic or excessive exposure to the peptide may promote learning problems and premature cognitive decline.

Keywords: hippocampus, neurotransmission, corticotropin-releasing factor, long-term potentiation, volume transmission, CRF, CRH receptor, $CRFR_1$

LEARNING AND MEMORY MUST BE INFLUENCED BY STRESS, NECESSITATING MEANS TO INFLUENCE SYNAPTIC TRANSMISSION: WHAT DO WE KNOW AND WHAT ARE SOME OF THE REMAINING GAPS?

Stress is generally defined as a signal conveying threat or potential threat (López et al., 1999; Kim and Diamond, 2002; McEwen, 2004; de Kloet et al., 2005; Joëls and Baram, 2009; Lupien et al., 2009), and, operationally as a signal that activates a specific brain system (Pacák and Palkovits, 2001). Stress of different types is common and pervasive. In addition, there is a strong evolutionary advantage to remembering and learning from threatening situations (McEwen, 1999). In contrast, the continuation of normal life requires forgetting severely stressful events, because such haunting memories might interfere with emotional health and with carrying out life's daily tasks, as is found in post-traumatic stress disorder (Wingo et al., 2010; Yehuda et al., 2010). Therefore, it is not surprising that stress has been found to be a powerful modulator of synaptic plasticity and memory (Kim and Diamond, 2002; de Kloet et al., 2005; Joëls and Baram, 2009; Lupien et al., 2009; Sandi, 2011). In the context of this series, the overall focus is on the mechanisms by which stress affects the hippocampus in a time- and severity-dependent manner, with consequences that contribute to a cognitive and emotional health and disease. Thus, whereas acute stress (lasting seconds to minutes) may augment memory and related cellular processes, longer stress tends to impair hippocampus-dependent learning and memory (Kim and Diamond, 2002; de Kloet et al., 2005; Diamond et al., 2006; Joëls and Baram, 2009).

A remarkable body of work that focused on the basis of these effects of stress has centered on the roles of adrenal-derived corticoid stress hormones and on their signaling via glucocorticoid receptors (GRs) and, more recently, mineralocorticoid receptors (MRs) (Kim and Diamond, 2002; de Kloet et al., 2005; Lupien et al., 2009; Joëls and Baram, 2009; Krugers et al., 2010; Segal et al., 2010; Sandi, 2011; Yuen et al., 2011). In view of the fact that MR activation generally increases synaptic plasticity (Joëls and Baram, 2009; Krugers et al., 2010), and the relatively limited distribution of GR on hippocampal CA3 pyramidal cells that are highly vulnerable to stress (Magarinos and McEwen, 1995; Sanchez et al., 2000; de Kloet, 2004; Joëls and Baram, 2009), it is reasonable to consider potential additional factors that may contribute to the actions of stress on the cognitive functions taking place within the hippocampus.

Among the many factors that influence the effects of stress (e.g., type of stress, age, and gender of the involved brain), Time and Space are key. As mentioned, seconds-long stress improves learning whereas chronic, weeks-long stress perturbs both hippocampal function and structure. When and how does

the transition occur? Similarly, emerging evidence indicates that stress may affect the dorsal and the ventral hippocampus differentially (Maggio and Segal, 2009; Segal, 2010). In addition, stress may destroy dendritic spine within minutes and hours in hippocampus, yet increase complexity of dendrites in amygdala (Vyas et al., 2002). How is the spatial specificity take place? A large body of work, cited elsewhere in this monograph, has tackled these temporal and spatial issues. In the temporal domain, elegant studies have demonstrated rapid, non-genomic effects of MR and GR activation, followed by slower (hours to weeks) genomic actions. Rapid effects of neurotransmitters may translate to longer actions through influence on enzyme activity (reviewed in Joëls and Baram, 2009). Here we focus on an additional temporal solution: stress-provoked release of a neuropeptide within hippocampus. Neuropeptides classically function in the time-frame of seconds to a few hours depending, among other factors, on their degradation and reuptake (Koch et al., 1974). Similarly, peptides offer an attractive solution to the spatial conundrum of the actions of stress: unlike neurotransmitters, they are exuded into the neuropil that may bathe hundreds and thousands of synapses, providing a means to influence synaptic transmission of defined neuronal populations within a defined spatial domain (Fuxe et al., 1990; Agnati et al., 1995; Landgraf and Neumann, 2004; Nässel, 2009). In the current monograph, we describe the hippocampal corticotropin-releasing hormone (CRH) system and the action of this peptide on hippocampal structure and function. A key remaining challenge is to discover how the actions of neurotransmitters, corticosteroids and peptides interact to influence learning and memory in the stressed hippocampus.

THE CRH SYSTEM OF ADULT HIPPOCAMPUS: CELLS, RECEPTORS, AND MIS-MATCHED SYNAPSES

POTENTIAL SOURCES OF CRH EFFECTS IN THE HIPPOCAMPUS

CRH is expressed within adult hippocampus and is released locally during stress (**Figure 1**, and see below). However, the peptide is also released within the amygdala (Roozendaal et al., 2002), locus ceruleus (Valentino and Wehby, 1988; Snyder et al., 2012) and other brain regions. Because this peptide can travel long distances within the brain (Bittencourt and Sawchenko, 2000), an extra-hippocampal source and transport of the peptide from distal brain regions to act on hippocampal $CRFR_1$ receptors cannot be excluded. However, organotypic cultures of the hippocampus have helped clarify the source of endogenous CRH influencing hippocampal neuronal structure. Growing these cultures (where other brain regions are not included) in the presence of selective blockers of CRH receptor type 1 (the receptor most highly expressed in the hippocampal formation), has resulted in abnormal dendritic growth. Dendritic branching is exuberant and total dendritic length is increased under these conditions, suggesting a role for endogenous *hippocampal* CRH in selective pruning or sculpting of the dendritic tree of hippocampal pyramidal cells. Because dendrites may grow or die-back (atrophy), as a function of activity of excitatory synapses located on dendritic spines, a potential mechanism of the effects of CRH on dendritic structure is via influencing the integrity of such spines (see below). In addition, the structure of dendritic trees of mice lacking the $CRFR_1$ receptor is abnormal, with similar exuberant branching (Chen et al., 2004a, 2008). Interestingly, this is not found in mice lacking $CRFR_1$ only in principal forebrain neurons (Wang et al., 2011a), though the dendritic trees of these mice seem to be resistant to chronic stress induced atrophy. Taken together, available data largely support the idea that the main source of the CRH that activates $CRFR_1$ within hippocampus is the hippocampus itself.

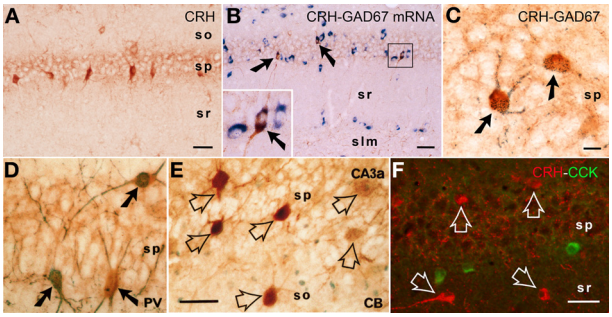

FIGURE 1 | CRH is expressed in interneurons within the hippocampal pyramidal cell layer. (A) CRH-immunoreactive (ir) neuronal somata in the pyramidal cell layer of area CA1. **(B,C)** All CRH-ir neurons in the pyramidal cell layer in CA1 area are GABAergic interneurons: they co-express the GABA synthesizing enzyme glutamic acid decarboxylase (GAD)-67 at both mRNA and protein levels, using immunocytochemistry coupled with *in situ* hybridization (GAD67, blue), and dual-labeled immunocytochemistry (CRH, brown; GAD67, black blue), respectively. Arrows indicate the dual-labeled neurons. **(D–F)** Many CRH-ir neurons in the hippocampus co-express parvalbumin (PV); none co-express calbindin D-28k (CB) or cholecystokinin (CCK). Solid arrows indicate the dual-labeled neurons, and empty arrows denote single-labeled CRH neurons. Abbreviations: so, stratum oriens; sp, stratum pyramidale; sr, stratum radiatum; slm, stratum lacunosum-moleculare. Scale bars = 75 μm **(A,B,F)**, 25 μm **(C)**, and 50 μm **(D,E)**. Reproduced, with permission, from Chen et al. (2004b) **(B)** and Yan et al. (1998) **(D,E)**.

WHO ARE THE HIPPOCAMPAL CRH-EXPRESSING CELLS, AND WHAT TYPE OF SYNAPSES DO THEY FORM?

CRH is produced in several populations of cells in the developing hippocampus (Yan et al., 1998; Chen et al., 2001), including Cajal-Retzius cells (Chen et al., 2001). In *adult* rodent hippocampus, the large majority of peptide is synthesized and contained within interneurons residing in the pyramidal cell layers of areas CA1 and CA3 (Sakanaka et al., 1987; Yan et al., 1998; Chen et al., 2001; Ivy et al., 2010) (**Figure 1**). CRH-expressing cells universally express the GABA synthetic enzyme GAD (**Figures 1B,C**), and include parvalbumin co-expressing basket cells (**Figure 1D**). Interestingly, there is no co-localization of CRH with calbindin D-28k (**Figure 1E**) or with cholecystokinin (**Figure 1F**).

The release site and mode of travel of CRH to target receptors are not fully understood. Light microscopy demonstrated a typical network of CRH-containing axon terminals surrounding the cell bodies of pyramidal cells (**Figure 2A**). In addition, both light and electron microscopy revealed that CRH is stored in axon terminals (**Figures 2B–F**) and released from axon terminal-vesicles surrounding the cell bodies and axon initial segments of pyramidal cells (Yan et al., 1998; Chen et al., 2001). These perisomatic release sites are >100 μm away from the location of the $CRFR_1$ receptors on dendritic spines in stratum

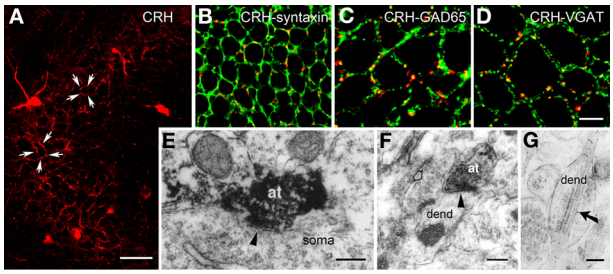

FIGURE 2 | CRH is located in GABAergic axonal terminals. (A) CRH-ir axon terminals form dense perisomatic baskets (arrows) around pyramidal cells in hippocampal area CA3. **(B)** CRH immunoreactivity localizes to pre-synaptic terminals, demonstrated by dual-labeled immunocytochemistry for CRH and for the pre-synaptic marker syntaxin. **(C,D)** CRH-containing terminals are GABAergic boutons as indicated by overlapping immunoreactivities of CRH and GAD65 **(C)** and of CRH and the GABA synaptic vesicular transporter VGAT **(D)** in axon terminals. **(E)** CRH-ir axon terminals (at) form axosomatic symmetric synapses (arrowhead) with pyramidal cell body (soma). **(F)** CRH-ir axon terminals form axodendritic asymmetric synapses (arrowhead) with dendrites (dend). Empty arrow indicates a bouton containing CRH-negative vesicles. **(G)** Electron micrograph demonstrating CRH-ir gold particles (arrow) within the dendrite, but not within vesicles. Scale bars = 50 μm **(A)**, 10 μm in **(D)** (25 μm for **B** and 12.5 μm for **C**), and 0.2 μm **(E–G)**. Reproduced, with permission, from Chen et al. (2004b) **(B–D)** and Yan et al. (1998) **(E)**.

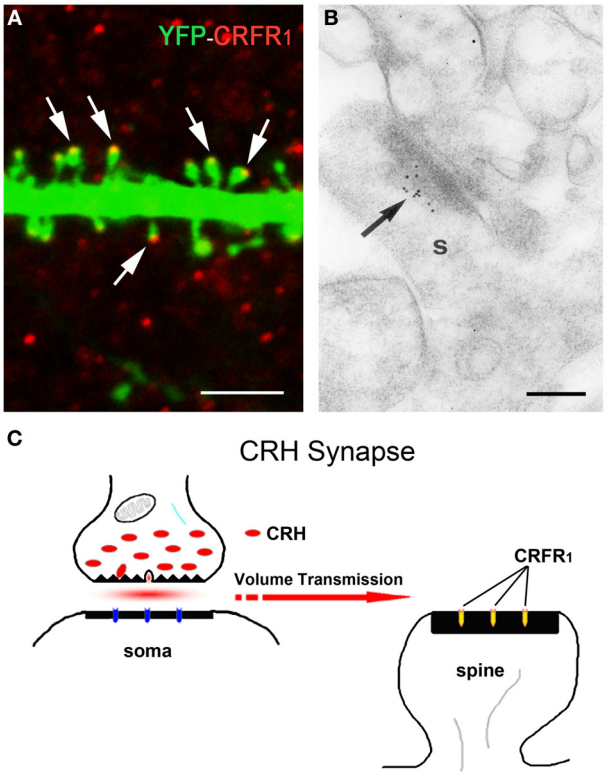

FIGURE 3 | The post-synaptic location of the CRH receptor $CRFR_1$ on dendritic spines. (A) The CRH receptor $CRFR_1$ (red) is located at the dendritic spine heads, as shown by confocal microscopy of CA3 pyramidal neuronal dendrite (green) from a YFP-expressing mouse. Arrows denote spine heads expressing the receptor. **(B)** Electron micrograph showing $CRFR_1$-immunogold particles (arrow) concentrated at the post-synaptic density (PSD) of an asymmetric (excitatory) synapse on a dendritic spine (s) in stratum oriens of hippocampal area CA3. Very few gold grains were observed elsewhere. **(C)** A cartoon depicting the concept of the mis-matched CRH synapse: pre-synaptic elements (axon terminal and boutons) are GABAergic (**Figure 1**), whereas post-synaptic elements on dendritic spines are consistent with excitatory synapses (**Figure 3A**). CRH that is released from inhibitory pre-synaptic elements may migrate via volume transmission and act on the $CRFR_1$ receptor at relatively distant excitatory post-synaptic sites. Scale bars = 3 μm **(A)**, 0.1 μm **(B)**. Reproduced, with permission, from Chen et al. (2010) **(A)**, (2004b) **(B)**.

radiatum (**Figures 3A,B**). The possibility that CRH is released from interneuronal dendrites closer to the receptors is not supported by electron microscopy studies, which show no evidence for vesicular localization of the peptide in dendrites (**Figure 2G**). Instead, these data support the idea that CRH released from interneurons in the pyramidal cell layer diffuses locally (via "volume transmission") (Agnati et al., 1995) to target receptors on dendritic spines (**Figure 3C**). Remarkably, these data indicate that the hippocampal CRH synapse is "mis-matched": the release site (pre-synaptic element) is an axon terminal of an interneuron (classically an element of inhibitory synapses), whereas the post-synaptic element resides on dendritic spines, and consists of dense post-synaptic elements, typical of excitatory synapses (**Figure 3C**).

CRH-$CRFR_1$ SIGNALING CONTRIBUTES TO THE EFFECTS OF STRESS ON HIPPOCAMPAL SYNAPTIC STRUCTURE AND FUNCTION

CRH may signal through two identified G-protein coupled receptor family members: CRH receptor type 1 ($CRFR_1$) and type 2 ($CRFR_2$) (Perrin and Vale, 1999). The distribution of $CRFR_1$ and $CRFR_2$ in the brain is different (Chalmers et al., 1995; Chen et al., 2000; Van Pett et al., 2000). In general, $CRFR_1$ is primarily responsible for mediating the synaptic actions of CRH on hippocampal principal cells (Schierloh et al., 2007; Refojo et al., 2011; Stern et al., 2011). In accord, $CRFR_1$ is amply expressed in hippocampal pyramidal cells (Chen et al., 2000, 2004b; Van Pett et al., 2000; Refojo et al., 2011), whereas little $CRFR_2$ expression is observed (Van Pett et al., 2000). Notably, in addition to the cell body, $CRFR_1$ is found on dendrites and within dendritic spines, the location of post-synaptic portions of excitatory synapses (Chen et al., 2004b, 2010). Indeed, a short stress that combining physiological and psychological components activates $CRFR_1$-containing pyramidal cells, indicated by increases in immediate early gene expression. This activation requires CRH-receptor signaling, because selective local blockade of $CRFR_1$ prior to the stress prevents this activation (Chen et al., 2004b, 2006). Of note, $CRFR_1$ signaling may be required for hippocampal plasticity even in the absence of stress: synaptic potentiation is abnormal in hippocampal slices from mice lacking $CRFR_1$ (Schierloh et al., 2007), and these mice have learning deficits (Contarino et al., 1999).

ACUTE (SECONDS TO MINUTES) EFFECTS OF CRH ON SYNAPTIC TRANSMISSION AND MEMORY

In line with the activating and memory-promoting effects of acute stress, the actions of CRH in the hippocampus are generally

excitatory (Baram and Hatalski, 1998). Application of CRH to hippocampal slices *in vitro* increases the firing rates of pyramidal cells by suppressing the after-hyperpolarization (Aldenhoff et al., 1983), and in the presence of an excitatory stimulus, CRH augments this input (Aldenhoff et al., 1983; Hollrigel et al., 1998). In a physiological context, brief application of CRH *in vitro* primes and augments LTP (Blank et al., 2002; Refojo et al., 2011) through $CRFR_1$ signaling. *In vivo*, a short treatment with CRH directly into the brain enhances memory (Wang et al., 1998, 2000; Blank et al., 2002; Joëls and Baram, 2009; Refojo et al., 2011). A significant additional body of work (e.g., Chen et al., 2004b, 2006, 2010) now demonstrates that stress induces rapid release of endogenous, hippocampal-origin CRH into the hippocampal intercellular space (**Figure 4**), as found also within the amygdala (Roozendaal et al., 2002), locus ceruleus (Van Bockstaele et al., 1996) and cortex (Behan et al., 1995). Taken together these facts suggest that CRH, rapidly released upon the onset of stress, excites synapses, and augments synaptic plasticity. This adaptive mechanism promotes learning and remembering during threatening situations, which might be teleologically advantageous.

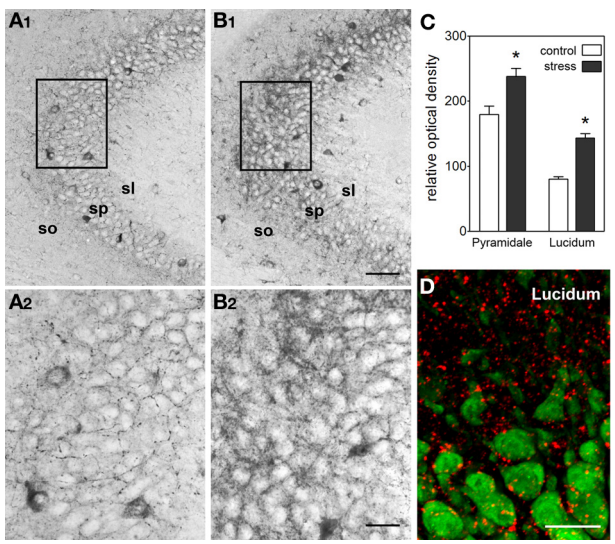

FIGURE 4 | Stress induces rapid release of endogenous CRH into the extracellular space within hippocampus. (A,B) Visualization of stress-induced release of endogenous CRH into the extracellular space (neuropil) in area CA3. Under control conditions **(A1,A2)**, there is little CRH-immunoreactivity outside of the cell bodies and terminals. In contrast, after a 30-min stress **(B1,B2)**, immunoreactive peptide is visible within the neuropil of the pyramidal cell layer and adjacent regions. See Chen et al. (2004b) for experimental details. Frames in **(A1,B1)** denote areas magnified in **(A2,B2)**, respectively, demonstrating the presence of CRH-immunoreactivity in the extracellular space. **(C)** Semi-quantitative analysis of CRH-immunoreactivity in presumed extracellular spaces of area CA3 ($n = 5$ animals, $^*P < 0.01$). **(D)** Stress-evoked release of endogenous CRH (red) into the extracellular space. NeuN (green) indicates CA3 pyramidal cells. Confocal image from a P18 rat sacrificed after a 30-min stress. Abbreviations: so, stratum oriens; sp, stratum pyramidale; sl, stratum lucidum. Scale bars = 60 μm in **(B1,A1)**, 20 μm in **(B2,A2,** and **D)**. Reproduced, with permission, from Chen et al. (2004b) **(D)**.

SUBACUTE, HOURS-LONG EFFECTS OF STRESS LEVELS OF CRH ON SYNAPTIC FUNCTION AND STRUCTURE

The effects of stress on synaptic function vary with the duration of the stress (among other parameters, including the severity, type and context of the stress, and variables intrinsic to the age and gender of the hippocampus itself). Given that CRH is released during stress, it is not surprising that the consequences of stress levels of CRH on hippocampal synapse structure and function vary with the duration of exposure. From the electrophysiological perspective, application of the hormone onto adult hippocampal slices has major effects on synaptic physiology: field EPSPs begin to decline ∼75 min into the infusion period, and short- and long-term synaptic plasticity is obliterated (Chen et al., 2012).

The neuroanatomical basis for this loss of synaptic function involves a loss of synapses. Specifically, CRH at presumed stress levels (Tringali et al., 2009) leads to retraction of dendritic spines that harbor post-synaptic elements of hippocampal excitatory synapses (Chen et al., 2008). This hippocampal effect of CRH supports prior findings in the amygdala (Matys et al., 2004; Bennur et al., 2007). Interestingly, although only a minority of dendritic spines are lost upon hours-long CRH (or stress), their loss results in profound memory impairment and loss of LTP. The magnitude of the functional deficits derives from the fact that spine loss is fairly selective to the subpopulation of thin dendritic spines (Chen et al., 2012). Among the diverse populations of dendritic spines, thin spines are called "learning spines" (Bourne and Harris, 2008; Holtmaat and Svoboda, 2009). They are most influenced by patterned neuronal activity that promotes learning. As these thin spines begin to express more glutamate receptors of the AMPA-GluR1 type, they are converted to mushroom type spines associated with memory storage. Hence, a loss of thin spines will disproportionately hampers the potential for the spine-plasticity process associated with learning and memory (Bourne and Harris, 2008; Maras and Baram, 2012).

The molecular mechanisms by which CRH provokes spine retraction are not fully understood. Whereas CRH-$CRFR_1$ interaction activates several signaling cascades (Swinny and Valentino, 2006; Stern et al., 2011), the activation of an actin-regulating Rho-GTPAse, a specifically RhoA seems to underlie CRH-induced spine loss: blocking RhoA-mediated function rescued dendritic spines from CRH-provoked loss (Chen et al., 2012).

In summary, whereas a short exposure to CRH promotes synaptic function and plasticity, longer exposure, especially to presumed stress-levels of the peptide produces effects on hippocampal neurons that would contribute to stress-related learning and memory impairments. The precise transition from positive to harmful effects of the peptide, and the interaction between length of exposure and CRH levels, as well as the interaction of CRH with glucocorticoid and adrenergic mediators require future study.

CHRONIC EFFECTS OF CRH ON HIPPOCAMPAL STRUCTURE AND FUNCTION

The effects of chronic stress on the integrity and neurotransmission of synapses have been extensively studied. Glucocorticoids, which are released peripherally in response to stress, can have

broad impacts on brain function (de Kloet, 2004; McEwen, 2004, 2011; Joëls, 2008; Lupien et al., 2009; Ulrich-Lai and Herman, 2009), whereas the local release of neurotransmitters and neuropeptides within the hippocampus itself provides for more spatially restricted modulation of specific synaptic populations (Joëls and Baram, 2009). The relative roles of glucocorticoids and CRH can be clarified in organotypic slice cultures or acute isolated hippocampal slices, which are not exposed to steroid hormones. Growing organotypic slice cultures chronically in the presence of exogenous CRH stunted dendritic growth (Chen et al., 2004a). These findings support a role for CRH in stress-related modulation of dendritic arborization and pruning.

A second approach to distinguish the requirement for CRH receptor signaling in effects of chronic stress on hippocampal synapses is via the use of transgenic mice, where the receptor is deleted in forebrain or hippocampus only. Adult mice lacking $CRFR_1$ in forebrain were relatively resistant to the deleterious effects of chronic social defeat stress (Wang et al., 2011a). Interestingly, the local deletion of this CRH receptor also protected adult mice from the adverse effects of chronic early life stress on learning and memory in adulthood (Wang et al., 2011b). Chronic early life stress, imposed by creating "simulated poverty" in the cage, results in cognitive problems and dendritic atrophy with loss of dendritic spines and synapses (Brunson et al., 2005). Infusion of $CRFR_1$ blocker immediately following this early life stress prevented the learning and memory defects, rescued LTP and restored the integrity of dendritic structure (Ivy et al., 2010). These findings provide direct evidence for a need for CRH-$CRFR_1$ signaling in the persistent effects of chronic early life stress on hippocampal synapses.

SUMMARY

The body of work reviewed above suggests that, in addition to canonical stress hormones, hippocampal CRH tunes synaptic transmission during stress, influencing memory. In addition, stress is associated with high levels of CRH at hippocampal synapses, and long exposures to these levels result in neuroanatomical and functional defects of hippocampal function. Teleologically, rapid local release of the neuropeptide is adaptive, promoting excitation, and enhanced synaptic function during acute stress. The consequences of protracted elevation of CRH levels during chronic stress are likely maladaptive, providing a potentially treatable cause of stress-related cognitive problems. Challenges in the field include a better understanding of the effects of CRH during relatively short stresses that are common in modern life: namely, those lasting for several hours, with combined physiological and psychological components. A second topic requiring study is the degree and nature of the interaction among concurrently acting stress hormones: glucocorticoids, neurotransmitters, and CRH. How these mediators function, and how they interact in molecular and cellular terms, is a key enigma that impedes our full understanding of the effects of stress on synaptic neurotransmission within the hippocampus.

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