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Corticotropin Releasing Factor in Neuroplasticity

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Abstract

Stress is among the strongest signals promoting neuroplasticity: Stress signals, indicating real or perceived danger, lead to alterations of neuronal function and often structure, designed to adapt to the changed conditions and promote survival. Corticotropin releasing factor (CRF) is expressed and released in several types of neuronal populations that are involved in cognition, emotion and the regulation of autonomic and endocrine function. CRF expressing neurons undergo functional and structural plasticity during stress and, in addition, the peptide acts via specific receptors to promote plasticity of target neurons.

Keywords

CRF; hippocampus; hypothalamus; neuropeptide; synapse; plasticity; stress; memory; epigenetics

1. Introduction and scope

Stress is among the strongest signals promoting brain plasticity. A vast body of work has demonstrated that stress signals, indicating real or perceived danger, lead to alterations of neuronal function, and often structure, designed to adapt to the changed conditions and promote survival (Christoffel et al., 2011; McEwen, 2012; Wosiski-Kuhn and Stranahan, 2012). These crucial changes take place at time scales ranging from seconds to months, and are mediated by a complex set of both central and peripheral mediators that together constitute the stress response. Stress-activated mediators have traditionally included neurotransmitters (norepinephrine, serotonin and others), and steroid hormones (cortisol in humans, corticosterone in rodents). The discovery and isolation of corticotropin releasing factor (CRF) by Wylie Vale and his team uncovered the nature of the enigmatic hypothalamic factor that stimulated ACTH release (Vale et al., 1981). In addition, Wylie and his group demonstrated the presence of the peptide in a number of brain regions outside of the hypothalamus and its neurotransmission functions, adding an important element of complexity to the intricate array of stress mediators (Vale et al., 1983). CRF is a neuropeptide, a class of molecules that often demonstrates distinct temporal and spatial action domains (Swanson et al., 1983; Landgraf and Neumann, 2004; Joëls and Baram, 2009; Maras and Baram, 2012), bridging the typical range of temporal actions of neurotransmitters and the genomic actions of steroid hormones. Whereas much overlap

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exists, the majority of neurotransmitters act via ionotropic or G-protein coupled receptors to evoke effects within millisecond to seconds. Neuropeptides overlap with this range in their synaptic effects (e.g.,Gallagher et al., 2008), but can also act more slowly, likely via polysynaptic (Hollrigel et al., 1998) or non-synaptic pathways (Landgraf and Neumann, 2004; Valentino and Van Bockstaele, 2008, Refojo 2011). The slower time-scale might result from the more long-distance travel of the peptide via volume transmission (Bittencourt and Sawchenko, 2000; Agnati et al., 2010). The time-scale of the action of peptides, including CRF, also differs from the time-scale of steroid hormones. Whereas rapid nongenomic actions of corticosteroid hormones have been well-described (Roozendaal et al, 2010; Groeneweg et al., 2011), the fundamental actions of corticosteroids involve GR and MR mediated genomic effects that require hours. Peptides also occupy a distinct (though overlapping) spatial niche: Because they are often dispersed via volume transmission, neuropeptides such as CRF can affect simultaneously numerous neurons in a brain region (Roozendaal et al., 2002; Agnati et al., 2010) rather than act at single or a few synapses, yet they do not permeate the whole brain, as do steroid hormones.

Wylie Vale isolated CRF from the hypothalamus and initially focused on the role of this peptide in promoting synthesis and release of ACTH from the pituitary gland (Brown et al., 1982; Gibbs and Vale, 1982; Rivier et al., 1982), In addition to the hypothalamus, well discussed in other manuscripts within this collection, Wylie's group (Swanson et al., 1983) as well as others, found that CRF is expressed or acts in the amygdala (Roozendaal et al., 2002; Gallagher et al., 2008; Regev et al., 2012), hippocampus (Lee et al., 1993; Chen et al., 2001a; Refojo et al, 2011; Chen et al., 2013), cortex (De Souza et al., 1986; Behan et al., 1995a; Gallopin et al., 2006), , inferior olive (Chang et al., 1996), locus coeruleus (Valentino and Van Bockstaele, 2008) bed nucleus of the stria terminalis (Dabrowska et al., 2011), and other areas affected by, or involved in, stress. Importantly, CRF receptors type-1 (CRFR1) and type-2 (CRFR2) are found on target neurons (Van Pett et al., 2000; Reul and Holsboer, 2002), and within specific subcellular compartments (Reyes et al, 2008; Chen et al, 2012), enabling complex and fine-tuned effects of CRF on target neurons throughout the brain.

Thus, CRF is an important component of the complex set of stress-mediators, allowing the brain to mount the entire spectrum of the stress response, ranging from immediate attention and strategic decisions, which are important for survival in the short-term, to storage of information about a stressful situation, which is advantageous in the long-term.

This manuscript focuses on CRF and neuroplasticity. Neuroplasticity may be defined as a long-lasting change in neuronal structure and/or function in response to a trigger. It is commonly believed that both structural and functional plasticity involves altered expression, transport and function of numerous genes in concert. Long-lasting neuroplasticity often derives from epigenetic mechanisms: enduring changes in chromatin structure that influence the presence and degree of transcription of genes and gene families. Here we discuss the CRF neuron in both hypothalamus and hippocampus. We describe how CRF neurons undergo functional and structural plasticity and, in addition, how the peptide acts via specific receptors to promote plasticity of target neurons.

2. Plasticity of the hypothalamic CRF neuron

Hypothalamic CRF coordinates neuroendocrine, autonomic and behavioral responses to stress (Brunson et al., 2001; Coste et al., 2001; Bale and Vale, 2004; de Kloet et al., 2005; Joëls and Baram, 2009; Lightman, 2008; Valentino and Van Bockstaele, 2008; Zoumakis and Chrousos, 2010; Aguilera, 2011; Bonfiglio et al., 2011), and dysregulation of CRF neurons within the paraventricular nucleus of the hypothalamus (PVN) is found in several stress-related affective disorders (de Kloet et al., 2005; Lloyd and Nemeroff, 2011;

Flandreau et al., 2012). CRF expression in the PVN is regulated by a variety of factors including stress (Swanson and Simmons, 1989; Watts, 2005; Lightman, 2008). It is generally found that stress activates both CRF release as well as a rapid increase in transcription of the gene (Yi and Baram, 1994; Rivest et. al., 1995; Ma et. al., 1997; Tanimura and Watts, 1998; Dent et al., 2000; Ginsberg et al., 2003; Watts, 2005; Pace et. al., 2009; Osterlund and Spencer, 2011; Liu et al, 2012). Appropriate initiation and termination of CRF secretion and synthesis are crucial for physiological homeostasis (Coste et al., 2001; Bale et al., 2002; Liu and Aguilera, 2009; Aguilera and Liu, 2012). Therefore, the manner by which stress signals reach and activate CRF cells in PVN, and the nature of the regulation of CRF expression levels and release have been subjects of intensive investigation.

Here we focus on certain aspects of stress-related neuroplasticity of the hypothalamic CRF neuron: We describe how synaptic connectivity, which influences neuronal function, is altered by early-life experiences. This unique structural and functional synaptic plasticity initiates intracellular events within CRF neurons that constitute an additional, enduring functional and molecular neuroplasticity.

2.1. Structural neuroplasticity of the hypothalamic CRF neuron

It has been well established that early-life experience induces persistent neuroplasticity of the neuroendocrine stress system, characterized by reduced stress responses (Levine, 1967; Plotsky and Meaney, 1993; Avishai-Eliner et al., 2001a), increased resilience to depressive-like behavior (Meaney et al., 1991) and improved learning and memory (Liu et al, 2000; Fenoglio et al., 2005). This neuroplasticity can be induced by a brief daily separation of rat pups from the dam (handling) during the first weeks of life, a manipulation resulting in augmented maternal-derived sensory input upon the reunification of dam and pups (Liu et al., 1997; Fenoglio et al., 2006a; Korosi et al., 2010). At the level of the hypothalamic CRF neuron, reduced expression of the gene is found in adult rats experiencing handling-related augmented maternal sensory input (Plotsky and Meaney, 1993; Liu et al., 1997; Fenoglio et al., 2005). Experience-induced reduction of CRF expression is observed rapidly, already by postnatal day 9 (P9), preceding the lowered hormonal stress responses and the epigenetically-induced augmentation of hippocampal GR expression (Avishai-Eliner et al., 2001a; Weaver et. al., 2005). These observations suggest that plasticity of the hypothalamic CRF neuron, resulting in repressed gene expression, is an early and important component of the effects of enhanced maternal sensory input on the stress response.

Therefore, experiments were conducted to uncover the nature of the signals, derived from maternal activities, that reach CRF neurons. Experiments also explored the resulting changes (plasticity) of the hypothalamic CRF neuron. Because the CRF neuron is a component of a neuronal network activated by maternal care (Fenoglio et al., 2006a), we examined if its neuroplasticity consisted of altered excitatory and / or inhibitory synaptic input. These changes, in turn, may provoke repression of the *crf* gene.

Innervation of CRF neurons includes GABAergic and glutamatergic synapses (Boudaba et al., 1997; Miklos and Kovacs, 2002; Ziegler et al., 2005; Karsten and Baram, 2013), that signal via $GABA_A$ (Cullinan, 2000) and glutamate receptors (Aubry et al., 1996; Kiss et al., 1996; Di et al., 2003). In addition, functional synaptic plasticity of the CRF neurons in PVN has been extensively studied in the context of stress (e.g., Kuzmiski et al., 2010; see Levy and Tasker, 2012 for review). Using quantitative confocal and electron microscopy coupled with electrophysiology, we examined the effects of early-life experience on excitatory and inhibitory synapses innervating CRF neurons. We found no significant changes in GABAergic synapse number or function. In contrast, there was a significant reduction in both the number and function of excitatory, glutamatergic synapses on the CRF neuron. The majority of the neurochemical, structural and electrophysiological data suggested a

presynaptic reduction in release sites (Korosi et al., 2010). Hence, early-life experience promotes structural neuroplasticity of the CRF neuron, consisting of reduced excitatory drive onto this neuron because of reduced glutamatergic synaptic innervation. The hypothalamic CRF neuron is part of the stress network (Hatalski et al., 1998; Chen et al., 2001a; Jankord and Herman, 2008; Dedovic et al., 2009; Bonfiglio et al., 2011); therefore, this neuroplasticity should reduce CRF release and expression in response to stress.

2.2. Functional / molecular neuroplasticity of the hypothalamic CRF neuron following early-life experience, and the potential role of epigenetic mechanisms

Molecular plasticity of the CRF neuron, and specifically alteration of CRF expression, has been described in numerous contexts. Acutely, stress augments transcription of the *crf* gene (Tanimura and Watts, 1998; Baram and Hatalski, 1998; Dent et al, 2000; Chen et al., 2001b; Ritter et. al., 2003; Fenoglio et al., 2006b; Liu et al., 2012; Cope et al., 2013). However, at longer time frames, stress can either increase (Sterrenburg et al., 2011) or decrease (Pinnock and Herbert, 2001; Ivy et al., 2008; Rice, et al., 2008) CRF levels.

CRF levels are persistently reduced in rodents experiencing augmented early life maternal care (Plotsky and Meaney, 1993; Brunson, et al., 2001; Avishai-Eliner, et al., 2001a). Levels of CRF expression in parvocellular hypothalamic neurons contribute to the fine-tuning of the neuroendocrine response to stress because there is a relationship between the levels of CRF expression and peptide release in response to stressful signals. Therefore, we sought to elucidate how the persistent, life-long reduction in CRF expression, induced by augmented maternal care early in life, is initiated and maintained.

In terms of the initiation of repression of the crf gene, ongoing studies are focusing on the potential causal relationship of reduced excitatory synaptic input to CRF neurons and the reduction of CRF expression. The maintenance of the long-lasting repression of this gene likely involves epigenetic mechanisms, i.e., changes to the conformation of the chromatin around the crf gene (review by Szyf, 2013; Lucassen et al., 2013). Changes in DNA methylation at the promoter region of the CRF gene have been reported in view of the contribution of DNA methylation to transcriptional repression (McGill et al., 2006), an inverse relationship of promoter methylation and crf expression has been sought, and indeed found (Mueller and Bale, 2008; Elliott et al, 2010, Chen et al., 2012a). Surprisingly, in our hands, the study of crf promoter and intron methylation after early-life augmented maternal care failed to find increased methylation as a mechanism for the enduring repression of the crf gene (McClelland, 2011), and these findings are consistent with the emerging complexity of various types of DNA methylation and the relationship of these modifications to gene expression (Lister, et al., 2013). Considering alternative mechanisms to DNA methylation, and focused on the potential role of the transcriptional repressor neuron-restrictive silencing factor (NRSF; Mori et al., 1992; Palm et al., 1998), because of the presence of a functional binding site for this repressor within the *crf* gene (Seth and Majzoub, 2001). Augmented maternal care was found to increase NRSF levels in the hypothalamus (but not in thalamus, Korosi et al., 2010), and the NRSF bound the NRSE site on the crf gene intron. Thus, NRSF is an attractive molecule to mediate the epigenetic changes underlying the persistent molecular neuroplasticity of the *crf* gene- and likely of numerous additional stress-related genes.

Whereas there is a general agreement about the molecular neuroplasticity of the CRF neuron following optimal or augmented maternal care early in life (Plotsky and Meaney, 1993; Liu et al., 1997; Korosi and Baram, 2009), this is not the case for the consequences of adverse early-life experience on the CRF neurons and specifically on CRF gene expression. Maternal deprivation has led to an enhanced CRF expression in the PVN (Aisa et al., 2007; Chen et al., 2012a). In contrast, others have found a depletion of steady-state CRF

messenger RNA in P9 rat or mouse pups after a week-long chronic stress provoked by limited nesting and bedding material in the cage (Avishai-Eliner et al., 2001b; Rice et al., 2008). These diverse findings suggest that early-life adversity can influence the stress-sensitive CRF neurons in multiple ways, and the distinct parameters involved (e.g., intermittent vs. continuous stress, patterns of maternal behavior [Baram et al., 2012]) as well as the cellular and molecular mechanisms, deserve further study.

3. CRF contributes to stress-induced neuroplasticity of learning and memory

3.1. Role for CRF in stress-induced memory problems

Stress is prevalent and unavoidable. It is biologically important because it enables both rapid and delayed adaptive processes to a changing environment. The adaptive importance of remembering threatening or dangerous events allows learning from them, which promotes survival. Because the hippocampus is a key brain region for learning and memory, many of the effects of stress on these cognitive functions take place within the hippocampus.

The effects of stress on hippocampal structure and function are bi-directional. Acute or short stress, lasting seconds to minutes, enhances hippocampal function by augmenting synaptic plasticity through a variety of mediators and mechanisms (Blank et al., 2002; Joëls and Baram 2009; McEwen and Gianaros, 2011). However, these same mechanisms, when activated intensely or for a prolonged period, may render the hippocampus vulnerable to the detrimental effects of chronic or severe stress (Joëls and Baram, 2009; Ulrich-Lai and Herman, 2009). Thus, the effects of stress on hippocampal functions are complex, depending on whether the stressful stimulus is mild or severe, acute or chronic, and on its perception as controllable and predictable vs. unpredictable and uncontrollable.

Recent studies have uncovered an important role for CRF in the effects of stress on learning and memory, and specifically the effects of stress on hippocampus- dependent learning. For example, blocking the ability of CRF to interact with its receptor attenuated the adverse effects of hours-long stress on memory (Chen et al., 2010), and mice lacking the CRFR1 were resistant to the pervasive effects of chronic early-life stress (Wang et al., 2011a) and chronic social stress (Wang et al., 2011b) on memory.

3.2. Hippocampal CRF: origins and targets

The studies cited above indicate that there is a role for CRF, acting on CRFR1, in the effects of stress on hippocampal function. However, the source of the peptide is not completely resolved. CRF is expressed in both developing and adult rodent hippocampus (Sakanaka et al., 1987; Chen et al., 2001a). The peptide is secreted from the interneuronal axon terminals into the local synaptic space during stress (Chen et al., 2012b). CRF is also expressed and secreted during stress in the amygdala (Roozendaal et al., 2002), locus coeruleus (Valentino and Wehby, 1988; Snyder et al., 2012) and other brain regions. CRF was shown to reach many brain regions when injected into the cerebral ventricles (Bittencourt and Sawchenko, 2000), and to travel from the central amygdala nucleus to the adjacent basolateral nucleus (Roozendaal et al., 2002). The precise mechanism for this transport, and a potential role of the CRF binding protein, remain unclear (Behan et al., 1995b; Seasholtz et al, 2001; Chen et al., 2004). Whereas it conceivable that the source of CRF that influences hippocampal neurons during stress might be from other brain areas, two lines of evidence suggest that the origin of CRF that acts on CRF receptor within hippocampus is local. First, in organotypic cultures of the hippocampus (where other brain regions are not included), the presence of selective blockers of CRFR1 (the receptor most highly expressed in the hippocampal formation) provokes abnormal dendritic growth, suggesting a role for endogenous

hippocampal CRF in shaping hippocampal dendritic structure (Chen et al., 2004). Second, electron microscopy studies demonstrate that CRF is stored within releasable vesicle pools at axon terminals of CRF-expressing interneurons (although there are no CRF-containing vesicles in dendrites), consistent with the presence of canonical release machinery for CRF at axon terminals. These data suggest local release of endogenous hippocampal CRF from interneuronal axon terminals (Yan et al., 1998; Chen et al., 2012b). In sum, available evidence supports the notion that CRF is produced in populations of interneurons in the pyramidal cell layers of areas CA1 and CA3 (Sakanaka et al., 1987; Yan et al., 1998; Chen et al., 2001a; Ivy et al., 2010). All of the CRF-expressing cells observed in adult hippocampus seem to express GAD, the GABA synthetic enzyme. Many co-express the calcium binding protein, parvalbumin, typical of hippocampal basket cells within the pyramidal cell layer, but none co-express cholecystokinin, which defines a separate set of interneurons (Chen et al., 2012b). It is still not fully resolved how stress promotes secretion of CRF from axonal terminals of these interneurons, and how the peptide reaches its receptors.

3.3. Stress-induced, CRF-mediated neuroplasticity of hippocampal cells

The evidence above suggests that during stress, hippocampal neurons are impacted by several stress-mediators: glucocorticoids reach the hippocampus from the adrenal, and act via both glucocorticoid and mineralocorticoid receptors (McEwen, 1999; Kim and Diamond, 2002; Roozendal et al., 2003; Joëls and Baram, 2009). During stress, hippocampal synapses are impacted by neurotransmitters such as serotonin and norepinephrine, and, as shown above, by hippocampal CRF. Hence, it is likely that hippocampal CRF contributes to an orchestrated set of cellular and molecular events initiated by stress within hippocampal neurons, which promote plasticity.

The duration of stress is especially important in determining its effects on learning and memory (Zoladz and Diamond, 2008; Joëls and Baram, 2009; Joëls et al., 2011; McEwen and Gianaros, 2011): Stress (and CRF application) lasting for *minutes* alters the structural and functional properties of neurons in a manner that is distinct from observations after stress lasting for *hours*, although both of these time-frames often designate “acute” stress. Chronic stress, lasting days and weeks, exerts still more distinctive changes in hippocampal function and structure. How does CRF contribute to these distinct, time-dependent effects of stress on memory?

During minutes-long stress, CRF release potentiates synaptic plasticity (Wang et al., 1998, 2000). It also leads to priming of long-term potentiation (Blank et al, 2002, 2003,). LTP is a cellular process that is generally considered to represent learning and memory (Larson and Lynch, 1986; Bliss and Collingridge, 1993). The ‘positive’ effect of CRF on hippocampal function during stress is supported by the fact that several hippocampus-dependent learning tasks are improved upon administration of CRF into the brain (Hung et al., 1992; Ma et al, 1999; Radulovic et al, 1999; Blank et al., 2002, 2003; Row and Dohanich, 2008). The mechanisms by which CRF influences synaptic function and memory at the seconds-to-minutes time window are not fully known. It is clear that CRFCRFR1 signaling is involved, because synaptic potentiation is attenuated in hippocampal slices from mice lacking CRFR1 (Schierloh et al, 2007), and, in addition, these mice have memory problems (Contarino et al, 1999). There is evidence for CRF-mediated increase of presynaptic glutamate release (Hollrigel et al., 1998), as well as enhanced postsynaptic excitability (Aldenhoff et al., 1983), potentially related to CRF-induced suppression of after-hyperpolarization (Aldenhoff et al., 1983). In addition, activation of several molecular cascades by crf receptor activation has been demonstrated, including specific kinases (Refojo et al., 2005; Punn et al., 2006)

beta-arrestins (Holmes et al., 2006; Oakley et al., 2007) and Rho GTPases (Swinny and Valentino, 2006; Chen et al., 2013).

A role for CRF in the effects of longer stress on hippocampus is suggested by several lines of evidence. First, genetic manipulation of CRF levels in hippocampus accelerated cognitive problems and structural decline in models of Alzheimer disorder (Dong et al., 2012). Indeed, overexpression of CRF in forebrain led to learning and memory defects (Wang et al., 2011a). CRF has also been implicated in dendritic and spine changes in hippocampus after a shorter stress, lasting several hours (Pawlak et al., 2005; Chen et al., 2013), and these effects involve both inter-cellular molecules such as nectin 3 (Wang et al., 2013) and intracellular mechanisms for destabilizing dendritic spines (Chen et al., 2013). Finally, exposing hippocampal explants to CRF chronically promotes loss of dendritic arborization (Chen et al., 2004). These data, suggest that CRF contributes to the established effects of hours-lasting and chronic stress on synaptic plasticity that underlies hippocampus-mediated learning and memory.

4. The hippocampal CRF neuron: target and mediator of cognitive effects of early life stress

Whereas stress during adult life leads to significant effects on neuronal function and on learning and memory, this type of neuroplasticity generally does not persist. In contrast, early-life stress may contribute to severe and enduring cognitive impairments (Nelson et al., 2007). These problems may emerge during adulthood, and seem to progress with age (Kaplan et al., 2001; Wilson et al., 2007). Is there a role for CRF in these long-lasting effects of early-life stress?

Early-life stress augments the expression levels of hippocampal CRF chronically: We generated chronic stress during postnatal days P2-P9 employing a naturalistic rodent model of limited resources by limiting the nesting and bedding material in the cages. This led to frequent sorties of the dam from the nest area, and to fragmented maternal care, with little effect on total care. Remarkably, the abnormal patterns and rhythms of maternal care generated chronic stress in the pups, as evident from adrenal hypertrophy and elevated plasma corticosterone (Avishai-Eliner et al., 2001b; Brunson et al., 2005). As adults, graduates of this early-life stress had apparent normal stress-hormone levels, but their memory was impaired on several tests (Brunson et al., 2005; Ivy et al., 2010).. These memory defects were associated with major deficits of LTP. The LTP defects were not global, but centered on the commissural / associational synapses in stratum radiatum of CA1 and CA3 (Brunson et al., 2005). Interestingly, the basis of the LTP problems was, at least in part, a loss of these synapses: the structure of the corresponding neurons was quite abnormal, including impoverished dendritic arborization and hence reduced numbers of dendritic spines and excitatory synapses (Brunson et al, 2005; Ivy et al., 2010; Wang et al., 2011a).

There is evidence that CRF contributes to the abnormal synaptic plasticity and synaptic loss generated by early-life stress: As mentioned, expression levels of hippocampal CRF were chronically augmented in this model (Fenoglio et al., 2006b; Ivy et al., 2010). In addition, selective blocking of central CRFR1 receptors during the week that followed the early-life stress period sufficed to abolish deficits in hippocampus-dependent memory, LTP and dendritic structure in selective regions of hippocampal CA1 (Ivy et al., 2010). These mechanistic studies support the role of CRF in these effects. Further support for a role of CRF in the effects of early-life stress on hippocampal structure and function is apparent from the fact that mice with a conditional forebrain CRFR1 knockout were resistant to the effects of chronic early-life stress (Wang et al., 2011a). Interestingly, the consequences of

chronic early-life stress were reproduced by simply over-expressing CRF postnatally in forebrain neurons (Wang et al., 2011a). Together, these studies demonstrate that functional, structural and molecular changes evoked by early-life stress are at least partly dependent on CRF over-activity via forebrain CRFR1 signaling.

It is intriguing to consider potential adaptive aspects of these neuroanatomical and functional changes. A cumulative stress hypothesis suggests that adults experiencing chronic early life stress might be more vulnerable to future stress (McEwen 2012; Nederhof and Schmidt, 2012). In contrast, a match-mismatch theory might suggest that the loss of memory processing capacity of adults subjected to chronic stress early in life might prepare them to an adult life fraught with stress. Reduced memory of stressful occurrences could be protective in this context (Wang et al, 2011a).

An important question with clinical significance involves the time frame of the actions of early life stress and the increased levels of CRF, and their potential reversibility. Two alternative scenarios are possible:

1. The “Critical Period’ hypothesis posits that the effects of early-life stress on hippocampal structure and function require excessive CRF-CRFR1 signaling during a critical period of brain programming within the first three weeks of life (Bale et al., 2010). If this hypothesis is true, then the first few postnatal weeks are the only period when intervention can prevent the detrimental effects of early-stress on hippocampus; after this time-period, the consequences of early-stress are programmed for life (Fig1A).
2. “Progressive” Hypothesis: Early-life stress sets in motion progressive molecular events that result in cognitive defects during adulthood, and perhaps an acceleration of aging-related cognitive decline (Ivy et al., 2010). In this scenario, blocking CRF signaling later in life might still prevent the negative outcomes resulting from early-life stress (Fig1B).

Existing data support both hypotheses: The resistance of mice with a conditional knockout of the CRFR1 gene to chronic early-life stress supports the progressive hypothesis, because these receptors, repressed via a CaMKinase II mechanism, are still expressed during the first 10 days of life, the period of chronic stress. In addition, in wild-type mice and rats, the progressive emergence of cognitive problems and the progression of the hippocampal cell injury also support the idea that chronic early-life stress induces progressive functional and structural changes in the hippocampus. This is likely to be at least in part via increased expression levels of CRF.

In support of the critical period scenario, whereas blocking CRFR1 immediately following the early-stress period (Ivy et al., 2010) reversed the effect of such stress, administration of CRFR1 blocker several months later had only a partial effect (unpublished observations). This result is expected if reversal of the consequences of chronic early-life stress was not possible beyond a ‘critical period’ (Figure 1).

5. Summary

Since the isolation and characterization of CRF by Wylie Vale, numerous studies--by his group and many others-- have demonstrated the importance of this peptide and its significance for myriad physiological as well as pathological conditions. Remarkably, the effects of CRF take place both peripherally, through its neuroendocrine functions, as well as within specific brain regions, as highlighted here.

CRF is a pivotal modulator of the stress response, and the effects of the peptide may be influenced by the amount / levels of peptide released as well as the duration of CRF action. Indeed, knock-out studies suggest that the two CRF receptors, R1 and R2 might contribute to the initiation of stress-related actions of the peptide and their termination, respectively (Bale et al., 2002; Bale and Vale, 2004; Coste et al., 2001). Further complexity derives from the fact that different targets of CRF seem to have distinct sensitivities to the peptide. Thus, low level, short CRF exposure promotes synapse function and plasticity, whereas high levels and long-duration exposure to the peptide results in elimination of synapses, as shown using live multi-photon imaging (Chen et al., 2013). This complexity endows CRF with both positive as well as detrimental effects. CRF promotes survival under stressful conditions (Denver et al., 2013), yet its excess can induce or contribute to a number of maladaptive consequences. Here we reviewed the role of CRF in neuroplasticity. Neuroplasticity underlies our ability to learn and to change, and is often helpful in the context of stress. However, excessive exposure to stress, e.g. chronic stress, severe stress or stress during critical periods in life can lead to maladaptive plasticity, accompanied by cognitive impairments. Together with other important components of the stress system (e.g. glucocorticoids; Timmermans et al., 2013), CRF plays a central role in these neuroplastic changes.

Whereas the majority of evidence for the role of CRF in neuroplasticity has arisen in rodent models, these studies carry important implications to human health and disease. CRF is chemically identical in rat and human, and a large number of human studies support a role for CRF in stress responses and coping (Bradley et al., 2008). Changes in CRF expression are found in aging (Behan et al., 1995a), depression (Raadsheer et al., 1995; Arborelius et al., 1999; Merali et al., 2006) and epilepsy (Wang et al., 2001), supporting a role for the peptide in neurological disorders. Together with the mechanistic animal studies discussed here, these findings suggest that a better understanding of the role of CRF in neuroplasticity should provide new avenues for developing intervention and perhaps prevention of stress-related cognitive and emotional disorders.

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Highlights

- Early-life experience contributes to plasticity of the neuroendocrine stress system.
- The CRF neuron in PVN is a key site of such plasticity via altered excitatory synapses.
- The hippocampal CRF neuron releases the peptide locally during stress.
- CRF contributes to stress-induced structural and functional hippocampal plasticity
- Chronic early-life stress persistently increases CRF expression in hippocampus.

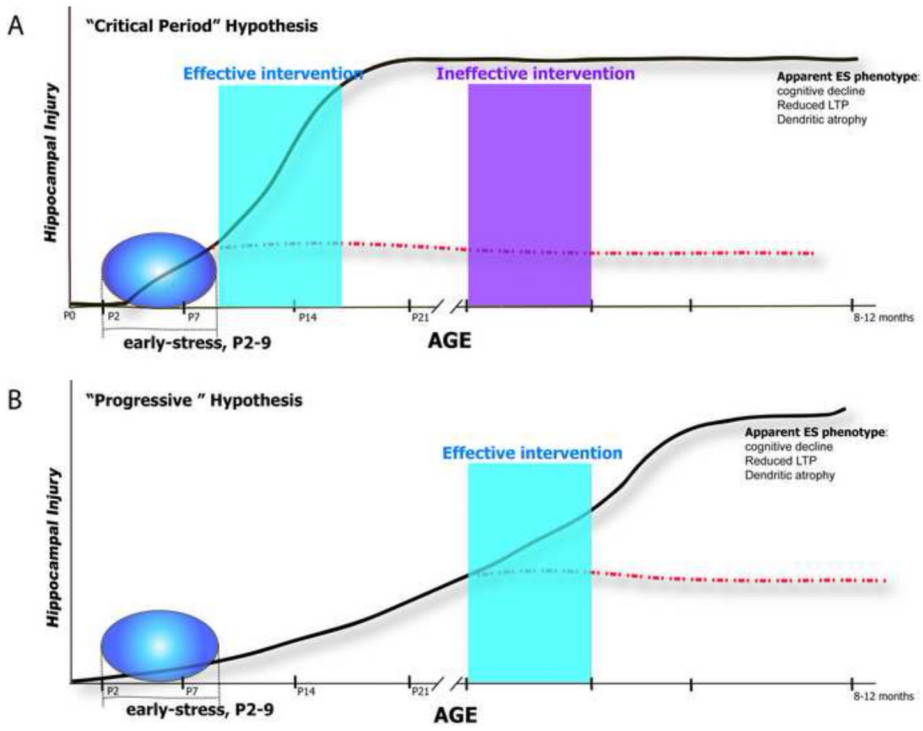

Figure 1. The long-term consequences of early-life stress may result from two alternative processes

(A) Chronic early-life stress (ES) may exert its long-term effects on hippocampal structure and function by interfering with hippocampal maturation during a vulnerable / critical developmental period; this possibility predicts that whereas interventions within the critical window will be effective (blue box), interventions initiated later in life will be ineffective (purple box). (B) Alternatively, ES may set in motion molecular cascades that progress over time to lead to functional / structural deficits apparent during middle age. This possibility predicts that therapeutic interventions initiated during young adulthood (blue box) will ameliorate the cognitive deficits.