UC Irvine
UC Irvine Previously Published Works

Title

The central corticotropin releasing factor system during development and adulthood

Permalink

Journal

ISSN

Authors

Korosi, Aniko
Baram, Tallie Z

Publication Date

DOI

Copyright Information

Peer reviewed

The central corticotropin releasing factor system during development and adulthood

Aniko Korosi and **Tallie Z. Baram**
Departments of Anatomy / Neurobiology and Pediatrics, University of California Irvine, Irvine, CA, USA.

Abstract

Corticotropin releasing factor (CRH) has been shown to contribute critically to molecular and neuroendocrine responses to stress during both adulthood and development. This peptide and its receptors are expressed in the hypothalamus, as well as in limbic brain areas including amygdala and hippocampus. This is consistent with roles for CRH in mediating the influence of stress on emotional behavior and cognitive function.

The expression of CRH and of its receptors in hypothalamus, amygdala and hippocampus is age-dependent, and is modulated by stress throughout life (including the first postnatal weeks). Uniquely during development, the cardinal influence of maternal care on the central stress response governs the levels of central CRH expression, and may alter the 'set-point' of CRH-gene sensitivity to stress in a lasting manner.

1. Introduction

Corticotropin releasing factor (CRH) is mediator of endocrine, autonomic, and immune responses to stress (Vale et al., 1981; Owens and Nemeroff, 1991; De Souza, 1995; Holsboer and Barden, 1996; Brunson et al., 2001a). CRH has also been implicated in the modulation of a wide range of behaviors including anxiety, as well as in arousal, motor function (Dunn and Berridge, 1990), and learning and memory (Blank et al., 2002; Fenoglio et al., 2006a). In these capacities as a central neurotransmitter in distinct brain regions, CRH is involved in both normal brain function as well as in pathological conditions including anxiety, depression (Nemeroff and Vale, 2005) dementia (Behan et al., 1995; Brunson et al., 2001b; Rehman, 2002) and addiction (Koob, 2006).

Several groups have demonstrated release of endogenous CRH from neurons within amygdala (Merali et al., 1998; Herringa et al., 2006) hippocampus (Chen et al., 2004b, 2006a), locus coeruleus (Curtis and Valentino, 1994; Kirby et al., 2000) and cerebellum (King et al., 1997). However, much remains to be determined about the nature of the endogenous CRH- CRH receptor unit: how is the peptide released? From which neurons? From dendrites or axon

terminals? How does the peptide reach its receptors? Is CRH transported by volume transmission or is there a specific 'CRH synapse' ? (Chen et al., 2004b). Where are the receptors located? What happens down-stream of CRHreceptor activation? What is the role of the CRH-binding protein in the central CRH system? Clearly, many questions about the CRH system remain unanswered. Here we focus on the available information and delineate the central CRH system, highlighting the functions of this peptide within the central nervous system (CNS) both in the adult and the developing organism. The data suggests that during development, CRH has additional roles that influence long-lasting plasticity within the CNS.

2. What is the central CRH system? Neuroanatomical distribution of CRH-expressing neurons and of the CRH receptors

2.1. CRH neuroanatomy

CRH mRNA and protein are widely but specifically distributed throughout the CNS (Merchenthaler et al., 1982; Swanson et al., 1983; Keegan et al., 1994; Arborelius et al., 1999; Chen et al., 2001a). A major site of CRH-containing cell bodies is the parvocellular portion of the hypothalamic paraventricular nucleus where CRH acts as neurohormone (Sawchenko and Swanson, 1985; Swanson and Simmons, 1989). CRH-expressing axons originating in these neurons project to the median eminence, where CRH is stored in the external layer. Hypothalamic CRH-expressing neurons belong to both the 'peripheral' and 'central' stress systems: Stress-evoked release of the peptide governs secretion of adrenocorticotropin releasing hormone (ACTH) from the pituitary, contributing to the peripheral, neuroendocrine stress response. In addition, regulation of CRH expression in these cells may be involved in setting the 'tone' of stress-related behaviors including anxiety, as well as learning and memory (Plotsky and Meaney 1993; Avishai-Eliner et al., 2001a; Fenoglio et al., 2006b). Thus, the CRH cells in the hypothalamic paraventricular nucleus may also be considered part of the 'central' stress system.

The presence of CRH has been demonstrated in selective regions in the brain. The peptide is found in neocortex and in limbic regions including central nucleus of the amygdala, dorsal and ventral part of the bed nucleus of the stria terminalis and hippocampus. High densities of CRH-immunoreactive neurons reside in locus coeruleus, dorsal and median raphe, periaqueductal gray, nucleus of the solitary tract and cerebellar complex (Merchenthaler et al., 1982; Swanson et al., 1983; Sawchenko and Swanson, 1985; Sakanaka et al., 1987; Koegler-Muly et al., 1993; Van Bockstaele et al., 1996; King et al., 1997; Morin et al., 1999; Chen et al., 2004b). Here we focus on the distribution and function of CRH and its receptors, CRF_1 receptor and CRF_2 receptor, in selected regions including the hypothalamic paraventricular nucleus, hippocampal formation and amygdala nuclei.

2.2. CRH receptors: distribution and function

CRH exerts its actions via a family of CRH receptors that includes two major characterized members: CRF_1 receptor and CRF_2 receptor (Perrin et al., 1993; Chalmers et al., 1995; Lovenberg et al., 1995), and CRF_2 receptor mRNA is translated in two functional splice variants, $CRF_{2}\alpha$ receptor and $CRF_{2}\beta$ receptor. CRH receptors belong to the superfamily of G-protein-coupled receptors characterized by the presence of a seven transmembrane domain. CRH receptor binding causes activation of adenylyl cyclase through a stimulatory G protein, resulting in an increased production of cyclic adenosine monophosphate (cAMP) that subsequently binds to the regulatory subunit of phosphokinase A. The subunit then dissociates from the catalytic subunit, thereby activating it, which results in phosphorylation of numerous proteins (McKnight et al., 1988) including transcription factors (Gonzalez and Montminy, 1989). In addition to the cAMP pathway, other second messenger pathways involving mitogen-

activated protein kinase, calcium ions and phospholipase C have been implicated in the actions of CRH (Rossant et al., 1999; Blank et al., 2003).

CRF_1 receptor mRNA expression is widespread in mature rodent brain (Potter et al., 1994; Van Pett et al., 2000). Regions expressing the receptor include olfactory bulb, cerebral cortex, certain amygdala nuclei, hippocampus, globus pallidus, red nucleus, pontine gray, substantia nigra, sensory and motor trigeminal nuclei, and cerebellum. At the protein level, CRF_1 receptor immunoreactivity is found in a localization pattern that generally overlaps the target regions of CRH-expressing projections and the distribution of CRF_1 receptor mRNA (see Chen et al., 2000, for the mouse). The $CRF_2\alpha$ receptor variant has been found in the CNS, where its distribution is more restricted than that of CRF_1 receptor. This receptor is found primarily in lateral septum, ventromedial hypothalamus, amygdala, dorsal raphe and bed nucleus of the stria terminalis (Van Pett et al., 2000). The $CRF_2\beta$ receptor variant is mainly present in non-neuronal cells, including in blood vessels (in brain and the periphery), heart, skeletal muscle and other organs.

The differential distribution of CRF_1 receptor and CRF_2 receptor already predicts that these receptors would exert different functions that are congruent with the established functions of the distinct brain regions where each one is located. Indeed, studies using mice deficient in one or both of these receptors, and those using selective receptor antagonists, have provided information about the distinctive function of the two CRH receptors. Thus, CRF_1 receptor is involved in the acute phase of the stress response, i.e., the activation of the hypothalamo-pituitary-adrenal (HPA) axis, whereas CRF_2 receptor seems to contribute to the recovery phase that involves gradual reduction of HPA axis activation (Coste et al., 2001; Reul and Holsboer, 2002). This idea is corroborated by the fact that CRF_2 receptor-knockout mice are hypersensitive to stress and have an increased anxiety-like behavior (Bale et al., 2000; Coste et al., 2000). For CRF_2 receptor, endogenous ligands might include, in addition to CRH, other members of the CRH family of peptides, including Urocortin 1 (Vaughan et al., 1995), that might thus contribute to the recovery phase of the stress response (Kozicz et al., 2004; Korosi et al., 2005).

3. Developmental neuroanatomy and regulation of CRH in rodent brain: hypothalamus

In view of the essential role of the stress response for normal function of the organism, a coordinate, progressive development of the stress circuit is required. Several studies in humans have demonstrated that early life trauma, such as childhood abuse or neglect, has lasting effects on parameters of the neuroendocrine stress circuit, and conveys major risk for the development of mood and anxiety disorders (Agid et al., 2000; Welberg and Seckl, 2001; Charney and Manji, 2004; Nemeroff, 2004). To understand the underlying mechanisms of vulnerability to stress-related disease, it is essential to study the development of the central components of the stress system. Thus in the following paragraphs we focus on CRH and CRH receptor expression, regulation (by glucocorticoids, stress, handling and maternal deprivation) and function during development, highlighting the brain areas playing key roles in this system.

3.1. The developmental profile and the regulation of CRH synthesis in the hypothalamic paraventricular nucleus

In rat, immunoreactive CRH is first found in fibers in the anterior region of the median eminence on day 18 of gestation (E18, Bugnon et al., 1982). Peptide expression increases, with a transient perinatal reduction (Bugnon et al., 1982; Daikoku and Hisano, 1992). CRH mRNA is first detectable in rat hypothalamic paraventricular nucleus on E17 (Grino et al., 1989; Baram and Lerner, 1991). In analogy to the CRH protein, hypothalamic paraventricular nucleus CRH

mRNA expression is robust during fetal days 18 and 19, decreases perinatally (fetal days 20 and 21, Grino et al., 1989; Baram and Lerner, 1991), and finally increases to reach adult levels by the end of the first postnatal week. In mouse hypothalamic paraventricular nucleus, CRH expression is first detected on E13.5, also decreases around the time of birth, then climbs to adult levels (Keegan et al., 1994; Schmidt et al., 2003).

3.2. Regulation of hypothalamic CRH expression by glucocorticoids

Onset of CRH synthesis and the levels of CRH mRNA in the hypothalamus during fetal life are not regulated by glucocorticoids (Baram and Schultz, 1990, 1992). In fact, manipulation of plasma corticosterone using pharmacological adrenalectomy (Plotsky and Sawchenko, 1987), despite the drastic reduction of glucocorticoid levels in the fetus and an increase in CRH mRNA in the pregnant dams, did not alter CRH gene expression in the fetal hypothalamus (Baram and Schultz 1990, 1992). This is fundamentally different from the well-documented negative feedback of glucocorticoids on CRH synthesis in adult (Herman et al., 1989; Imaki et al., 1991). The lack of alteration of CRH mRNA levels by glucocorticoid in the fetal rat is not due to the absence of glucocorticoid receptors because glucocorticoid receptor mRNA has been shown in the hypothalamic paraventricular nucleus as early as the 16th fetal day (Yi et al., 1994). The onset of glucocorticoid negative feedback effect on CRH gene expression commences at the end of the first postnatal week. This has been shown using both adrenalectomy (Grino et al., 1989) and by implanting corticosterone-containing cannula into the hypothalamic paraventricular nucleus (Yi and Baram, 1993).

3.3. Regulation of CRH expression by acute and recurrent acute stress in the hypothalamus

A major component of the mature stress response is the transient upregulation of hypothalamic CRH synthesis associated with expression of immediate early genes (Kovacs and Sawchenko, 1996). Stress leads to depletion of hypothalamic stores of CRH (Ixart et al., 1987) and to a compensatory increase of CRH mRNA levels in the hypothalamic paraventricular nucleus (Lightman and Harbuz, 1993). In immature brain, the first two postnatal weeks has been characterized by attenuated hormonal response and altered gene regulation. However throughout this period CRH is secreted in response to stimuli that are stressful to a neonatal rat (Yi and Baram, 1994), leading to elevation of plasma corticosterone. Starting (at the latest) on the sixth postnatal day, saline injection and cold exposure are capable of inducing rapid increase of CRH gene transcription within 2–15 minutes after the stimulus (Baram and Hatalski, 1998; Dent et al., 2000; Chen et al., 2001b). This activation of the CRH gene can be measured using heteronuclear CRH RNA, and, by the ninth postnatal day is sufficiently robust to result in increased steady-state CRH mRNA levels in the hypothalamic paraventricular nucleus (Yi and Baram, 1994; Hatalski et al., 1998; Dent et al., 2000; Chen et al., 2001b). Stress-induced activation of CRH mRNA transcription is consistent with compensatory upregulation of CRH gene transcription after enhanced secretion of the peptide from hypothalamic nerve terminals, as found in the mature rodent (Lightman and Young, 1989). In the immature rodent, acute stress-evoked CRH gene activation might be regulated by pCREB (Chen et al., 2001b), as found in the adult (Kovacs and Sawchenko, 1996), suggesting that *acute* stress regulates CRH gene transcription fundamentally in the same manner in immature and adult hypothalamic paraventricular nucleus. The effects of *recurrent* stress, however, differ by age: recurrent stress augments hypothalamic CRH levels in adult rodents (Harbuz and Lightman, 1989; Makino et al., 1995b). In contrast, recurrent cold stress in the immature (P10) rat results in hypothalamic paraventricular nucleus CRH expression levels that resemble those of unstressed controls (Hatalski et al., 1998). The mechanisms for this age-specific effect of recurrent stress are not fully resolved. Negative feedback via glucocorticoids, released upon the first stress, should suppress CRH expression, and are already functional at P10. However, the facilitatory effects of stress on CRH gene expression (Akana and Dallman, 1992, 1997),

acting likely via the amygdala (Bhatnagar and Dallman, 1998), may not be fully functional (Walker and Dallman, 1993; Brunson et al., 2001a).

Thus, acute stress activates neuroendocrine responses, including transcription of the CRH gene, throughout development. However, the regulation of CRH expression and function does differ in immature and adult rodents in response to several other stimuli, most notable of which is the exquisite and enduring response of the CRH gene to maternal care (Denenberg and Whimby, 1963; Levine, 1970,1994; Avishai-Eliner et al., 1995; Vazquez, 1998; Eghbal-Ahmadi et al., 1999; van Oers et al., 1999; Dent et al., 2000; Brunson et al., 2001a; Sanchez et al., 2001; Fenoglio et al., 2006b)

3.4. Effect of maternal deprivation, handling and chronic early life stress on CRH expression and function in the hypothalamic paraventricular nucleus

Early life experience induces enduring neuroplasticity of the HPA axis (Levine, 1957, 1967; Francis et al., 1999; Sanchez et al., 2001; Avishai-Eliner et al., 2002; Plotsky et al., 2005; Fenoglio et al., 2006b), including lasting alteration of the levels of CRH expression in the hypothalamic paraventricular nucleus. Several paradigms have been used to investigate the role of maternal input in these effects. These have either employed separation from the mother for up to 24 hours, or alteration of maternal behavior either by 'handling' or via limiting nesting materials for the dam during the first weeks of life.

1. Maternal separation for 24 h has been shown to either not influence (Avishai-Eliner et al., 1995), or reduce (Smith et al., 1997a) basal hypothalamic paraventricular nucleus CRH gene expression. In mice, CRH mRNA levels decrease after 8–24 h of deprivation (Schmidt et al., 2004). In response to acute stress, maternal deprivation leads to higher secretion of ACTH and glucocorticoid (Avishai-Eliner et al., 1995; Baram et al., 1997; van Oers et al., 1998; Dent et al., 2000) and rapid stress-induced transcription of the CRH gene (Baram and Hatalski, 1998; Dent et al., 2000).

2. Daily brief (15 min) separations from the mother between postnatal days 2–7 (Denenberg and Whimby, 1963), 2–9 (Avishai-Eliner et al., 2001a; Fenoglio et al., 2006b) or 2–21 (Levine, 1967; Plotsky and Meaney, 1993), result in an adult phenotype of reduced stress response (Levine, 1957; Plotsky et al., 2005), reduced basal expression of CRH in the hypothalamic paraventricular nucleus, and increased hippocampal expression of glucocorticoid receptor (Plotsky and Meaney, 1993; Avishai-Eliner et al., 2001a). Handling enhances dam-pup interaction by provoking maternal sensory simulation of pups immediately after their return to the home cage (Brown et al., 1977; Fenoglio et al., 2006b). Enhanced maternal care, attributable to either natural variation (Liu et al., 1997; Caldji et al., 1998) or induced experimentally by handling (Plotsky and Meaney, 1993) has been shown to lower CRH expression in the hypothalamic paraventricular nucleus, reduce hormonal responses to stress, and increase hippocampal glucocorticoid receptor levels (Avishai-Eliner et al., 2001a), changes collectively termed reduced HPA axis tone. Further insight into the mechanisms by which handling (or maternal input) influences CRH gene expression and the HPA axis tone has come from the finding that CRH and glucocorticoid receptor glucocorticoid receptor expression changes do not develop together but arise sequentially. Reduction of CRH expression in hypothalamic paraventricular nucleus occurs already by P9, developing as the first change of the several that occur at different levels of the HPA axis (Avishai-Eliner et al., 2001a; Fenoglio et al., 2006b). This supports a role of this gene regulation in the molecular cascade bridging handling-evoked maternal care and long term neuroplasticity of the HPA axis. CRH downregulation however does not occur after single handling maneuver but requires recurrent handling, even though already a single handling event elicits a burst of maternal stimulation of the pups (Fenoglio et al., 2006b).

3. Chronic early life "emotional" stress: Limiting the amount of nesting material constitutes a continuous stressor for the dam, leading to fragmented maternal care, which, in turn, stresses the pups (Gilles et al., 1996; Avishai-Eliner et al., 2001b). Thus the use of this paradigm from P2–P9 constitutes a chronic psychological early life stress. In fact, this paradigm evokes changes in the pups that are typical for chronic stress (Avishai-Eliner et al., 2001b): increased plasma glucocorticoid, increased adrenal weight and modestly reduced body weight (Hauger at al., 1988; Harbuz et al., 1992; Anderson et al., 1993). By the end of this week of stress (P9) CRH mRNA expression in the hypothalamic paraventricular nucleus of the early life stress group is significantly reduced compared to undisturbed controls both in rats (Avishai-Eliner et al., 2001b) and mice (Burgdorff et al., Soc. Neurosci. Abst, 2007). Reduced CRH expression may involve altered glucocorticoid negative feedback and/or increased CRH release concomitant with a failure of acute stress-induced facilitation of CRH production (Avishai-Eliner et al., 2001b). This depletion of hypothalamic CRH mRNA in the chronically stressed immature rodent differs from the adult situation (increased, decreased or unchanged, depending on the stress paradigm; Hauger et al., 1988; Harbuz et al., 1992; Anderson et al., 1993), indicating that the stage of development of the limbic-hypothalamic-pituitary-adrenal axis plays a critical role in the processes triggered by this chronic stress. Showing this reduction of CRH expression already at P9 is consistent with the concept that immature rat has a more rapid time course of adaptation to chronic stress which may be specific to this age (Dallman, 2000).

4. Developmental neuroanatomy and regulation of CRH in rodent brain: Hippocampus

While hypothalamic CRH plays a neuroendocrine role, activated upon physiological stressors (also referred to as 'reactive' and 'physical'), in higher brain centers CRH is an important mediator of psychological stressors (also termed 'anticipated' and 'emotional'; Herman and Cullinan, 1997). These stressors activate higher-order limbic pathways that contribute to the central stress circuit (Herman and Cullinan, 1997) which includes the amygdala (McGaugh et al., 1996; Hatalski et al., 1998; Dayas et al., 2001) and the hippocampus (Meijer and de Kloet, 1998; Deak et al., 1999; Hatalski et al., 2000; Kjelstrup et al., 2002; Joels et al., 2004; Herman et al., 2005; Chen et al., 2006a; McEwen and Milner, 2007; and many others). During acute challenge, stress signals converge on the amygdala (Roozendaal et al., 1997,1998), and selected stress signals reach the hippocampus (Wang et al., 1998; Hatalski et al., 2000; Blank et al., 2002). The hippocampus has crucial roles in learning, memory storage and retrieval and other cognitive functions, so that the effects of stress on the integrity of hippocampal structure and function has received much attention, as described in other chapters in this volume. Here we focus on 1) the development and regulation of the hippocampal CRH (2) the role of CRH in the effects of stress on hippocampal structure and function, and the distinction between the persistent effects of early-life stress on hippocampus versus the generally reversible effects of stress on mature hippocampus.

4.1 The developmental profile and regulation of CRH synthesis in hippocampus

Compared to the hypothalamus, CRH mRNA expression is low in developing hippocampus (Vazquez et al., 2006). However the increased resolution of immunocytochemistry has demonstrated that CRH immunoreactive neurons are present in the hippocampal formation of stress-free rats as early as P1 (Yan et al., 1998; Chen et al., 2001a). The number of CRH immunoreactive neurons increases progressively during postnatal development, peaking at P18 (Chen et al., 2001a). In adult hippocampus, most CRH expressing neurons are GABAergic (Swanson et al., 1983; Merchenthaler, 1984; Yan et al., 1998). CRH expressing interneurons are primarily basket cells that synapse on somata of hippocampal pyramidal neurons. This positions them strategically to significantly influence pyramidal cell activity and hippocampal

information flow. During development, a second, significant population of CRH expressing neurons can be distinguished, possessing the morphology of hippocampal Cajal-Retzius cells. Most of these non-GABAergic neurons disappear by the end of the second postnatal week (Chen et al., 2001a).

In adult rats, administration of the synthetic glucocorticoid dexamethasone does not influence CRH levels in hippocampus (Calogero et al., 1991), whereas steroid elimination via adrenalectomy significantly decreases CRH mRNA in immature CA1 neurons (Brunson et al., 2001b). CRH gene expression in adult hippocampus had not been found to correlate with stress (Makino et al., 1995a), but increases after kindling (Smith et al., 1997b). In the immature rat, prototypic physiological challenge that activates the HPA axis (cold exposure) does not alter CRH expression and does not induce fos expression in hippocampus. In contrast an up-regulation of hippocampal CRH mRNA has been shown following hyperthermia (Hatalski et al., 2000), that was associated with intense neuronal activation, and was blocked by the administration of sodium pentobarbital (a blocker of polysynaptic neurotransmission via interaction with the $GABA_A$ receptor; Hatalski et al., 2000). In concert with these observations, kindling and kainic acid-evoked seizures also increased CRH expression in hippocampus (Smith et al., 1997b). Psychological stress in adult (Smith et al., 1997a) and immature rat (Hatalski et al., 2000) increased CRH expression in hippocampus (Hatalski et al., 2000). These studies also demonstrate that hippocampal CRH expression is regulated independent of that in the hypothalamus.

Brunson and colleagues found that early-life chronic stress leads to enduring, life long elevation of CRH expression within the hippocampal CA3 area (Fenoglio et al., 2006a). Early life stress impairs hippocampus-mediated cognitive functions, and disrupts synaptic physiology and LTP (Brunson et al., 2005). One of the possible mediators of the effects of early life stress on hippocampal neurons is CRH. The notion that hippocampal CRH in immature rat may participate in the mechanism by which early life stress influences learning and memory long-term is supported by several lines of evidences. These include the age-specific abundance of CRH expressing neurons in the developing hippocampus, the chronic upregulation of hippocampal CRH expression by early life stress, and, as described in the paragraphs below, the release of hippocampal CRH by stress, the excitotoxic actions of this peptide on hippocampal dendrites and neurons, and abundance of CRH receptors during development.

4.2. CRH as a mediator of the actions of stress on hippocampal function

Psychological stress induces the release of endogenous hippocampal CRH (Chen et al., 2004b). CRH released by stress leads to the activation, measured by immediate early gene expression, of CA3 pyramidal cells, implicating endogenous CRH in the mechanism by which stress influences hippocampal pyramidal neurons. CRH excites hippocampal neurons, as evident from both in *vitro* (Aldenhoff et al., 1983; Hollrigel et al., 1998) and in *vivo* studies (Ehlers et al., 1983; Marrosu et al., 1988; Baram et al., 1992). Indeed, CRH administration early in life (P10) recapitulates the cognitive and LTP effects of early-life stress (Brunson et al., 2001b). This decline in hippocampal function in the CRH treated animals was progressive, and worsened over time. Importantly, the effects of early-life CRH occurred also in rats that were adrenalectomized prior to the experiment and maintained on low physiological corticosterone levels (Brunson et al., 2001b). In conclusion, in hippocampus, CRH modulates synaptic neurotransmission and in turn expression of the CRH gene is controlled by hippocampal circuit activation. Thus, this peptide contributes both to reversible effects of adult chronic stress, and to the enduring effects of early-life chronic stress, on hippocampal function.

5. Developmental neuroanatomy and regulation of CRH in rodent brain: Amygdala

The central nucleus of the amygdala is a key regulator of the stress response (Gray and Bingaman, 1996). CRH expressing neurons are found in the amygdala nuclei which are key components of the limbic stress circuit (Merali et al., 2004; Herman et al., 2005). Stress triggers the release of endogenous CRH in central nucleus of the amygdala, because administration of CRH antagonist into amygdala can attenuate stress-induced behaviors (Roozendaal et al., 2002). CRH mRNA levels within the amygdala can be already detected at P6 and gradually increases with age (Vazquez et al., 2006).

5.1. Regulation of CRH expression in the central nucleus of the amygdala by glucocorticoids, ACTH and stress

Administration of exogenous ACTH, or increasing endogenous ACTH levels by adrenalectomy downregulate CRH mRNA in central nucleus of the amygdala in P9–P11 rats (Brunson et al., 2001a). The ACTH (4–10) fragment infused i.c.v. also reduced CRH mRNA expression in central nucleus of the amygdala, even though it was devoid of any effects on plasma corticosterone, indicating that decreased CRH mRNA expression induced by ACTH is independent of steroid mediated mechanisms, and likely involves activation of the melanocortin 4 receptor (Brunson et al., 2001a). Glucocorticoids increase CRH gene expression in central nucleus of the amygdala of mature (Makino et al., 1994) and developing rats (Grino et al., 1989; Yi et al., 1993; Hatalski et al., 1998). In adult rat, expression of CRH mRNA in central nucleus of the amygdala is responsive to acute stress (Kalin et al., 1994). In the immature rat a single acute stress does not alter central nucleus of the amygdala CRH expression (Hatalski et al., 1998; Vazquez et al., 2006), but repeated stress does (Hatalski et al., 1998).

5.2 Age-specific regulation of central nucleus of the amygdala CRH expression: handling and maternal deprivation

CRH in the central nucleus of the amygdala may contribute to the role of this region in the integration of sensory signals from the mother (Eghbal-Ahmadi et al., 1999; Sanchez et al., 2001; Fenoglio et al., 2006b). CRH expression in central nucleus of the amygdala is enhanced by daily handling already by P6. By P9, enduring up-regulation of CRH mRNA in central nucleus of the amygdala is associated with similar changes in the bed nucleus of the stria terminalis (Hatalski et al., 1998; Fenoglio et al., 2004). This increase in CRH expression in central nucleus of the amygdala on P9 is associated with the reduced CRH expression in hypothalamic paraventricular nucleus. Possible mechanism underlying this independent and opposite effect on the two nuclei are the elevated levels of glucocorticoid after handling on P9 (Fenoglio et al., 2004). In fact, elevated glucocorticoid levels increase central nucleus of the amygdala and decrease hypothalamic paraventricular nucleus CRH gene expression in mature (Swanson and Simmons, 1989; Makino et al., 1994; Palkovits et al., 1998) and developing rats (Grino et al., 1989; Yi et al., 1993; Hatalski et al., 1998). After handling, no long-term increase of central nucleus of the amygdala CRH mRNA was observed (Plotsky and Meaney, 1993; Avishai-Eliner et al., 2001a). CRH mRNA expression is not altered by 24 h maternal deprivation (Vazquez et al., 2006).

6. Developmental neuroanatomy and regulation of CRH receptors in rodent brain

Within the brain CRH is synthesized and released into synaptic spaces where it can activate its receptors; therefore, the actions of this neuronal effector may be modulated via alteration

of CRH receptor expression or binding capacity. Thus the developmental pattern of expression of CRH receptors, their regulation and binding properties through development provide useful information regarding modulation of age specific roles of CRH in different brain areas.

6.1. The developmental profile of the CRH receptors in the rat brain

CRF_1 receptor mRNA distribution during development reveals several distinctive spatial and temporal patterns (Avishai-Eliner et al., 1996). In hippocampal CA1, CA2 and CA3a maximal (300–600% of adult) CRF_1 receptor mRNA levels are found on P6. In the amygdala, CRH receptor mRNA levels peak on the P9 (180% adult values). In the fronto-parietal cortex, a steady decline from high P2 levels results in adult levels by day 12.

Expression of the second member of the CRH receptor family, CRF_2 receptor is evident between fetal day 16 and 19 in ventromedial hypothalamus, lateral septum, amygdala nuclei, frontal cortex and habenula. These are joined by P1 by several hippocampal fields. CRF_2 receptor expression is fairly constant throughout development in the majority of these regions (Eghbal-Ahmadi et al., 1998), in contrast with CRF_1 receptor. The initial expression of CRF_2 receptor in the ventromedial hypothalamus, preceding detectable mRNA signal for CRH itself in the hypothalamic paraventricular nucleus (Altman and Bayer 1986; Grino et al., 1989; Baram and Lerner, 1991) suggests that the CRF_2 receptor may serve functions that are independent from activation by CRH during the early developmental period (e.g., cellular growth and differentiation). Alternatively, the CRF_2 receptor may be activated by a non-CRH ligand (e.g., Urocortin 1; Vaughan et al., 1995).

6.2. Regulation of CRH receptor expression

Acute stress increases CRF_1 receptor mRNA expression in Hypothalamic paraventricular nucleus and supraoptic nuclei of mature rat (Luo et al., 1994; Makino et al., 1995a,1997; Rivest et al., 1995; Bonaz and Rivest, 1998; Imaki et al., 2001), but not mouse (Imaki et la., 2003). Chronic stress reduces CRF_1 receptor mRNA in the hypothalamic paraventricular nucleus (Makino et al., 1995a; Iredale et al., 1996; Bonaz and Rivest, 1998). In immature rat, acute stress has a biphasic effect on CRF_1 receptor mRNA expression (Brunson et al., 2002) and chronic stress reduces expression of this receptor in CA1 and dentate gyrus (Avishai-Eliner et al., 2001b). CRF_1 receptor mRNA expression is upregulated in CA3 area of adult animals given CRH early in life (Brunson et al., 2001b). The reported effects of glucocorticoids on CRF_1 receptor mRNA expression in hypothalamic paraventricular nucleus are inconsistent (Makino et al., 1995a, 1997), but are generally in line with those of stress.

CRF_2 receptor mRNA in ventromedial hypothalamus is influenced by food deprivation in adults (Timofeeva and Richard, 1997; Makino et al., 1998), and reduced following maternal deprivation in infant rats (Eghbal-Ahmadi et al., 1997). However, during this age, maternal sensory input rather than food is the dominant regulator of this receptor's expression in ventromedial hypothalamus (Eghbal-Ahmadi et al., 1999). Glucocorticoids increase ventromedial hypothalamus CRF_2 receptor mRNA expression, but have no effect on expression of this gene in hypothalamic paraventricular nucleus (Makino et al., 1997,1998).

CRH itself may control CRF_1 receptor and CRF_2 receptor expression. Thus, exogenous CRH stimulates transcription of CRF_1 receptor in adult hypothalamic paraventricular nucleus (Imaki et al., 1996; Mansi et al., 1996) and in developing hippocampus and frontal cortex (Brunson et al., 2002). Whereas CRH has little effect on adult (Mansi et al., 1996) or immature (Brunson et al., 2002) CRF_2 receptor expression in rat, the peptide may play a role in regulating both CRF_1 receptor and CRF_2 receptor mRNA expression in mouse (Korosi et al., 2006).

6.3. Age-specific functions of CRH receptors

Whether CRF_1 receptor and CRF_2 receptor have unique developmental roles in addition to their established function as transducers of the effects of CRH-family ligands, is not currently known (Schmidt et al., 2004, 2006). However, several pieces of evidence support this concept.

1. CRF_1 receptor: mice lacking this receptor have abnormal shape of hippocampal neurons. Specifically, dendritic trees are exuberant and complex (Chen et al., 2004a). Whereas the presence of these changes has not yet been demonstrated in fore-brain restricted null mice, a direct role for CRF_1 receptor is supported by the fact that these abnormal dendritic trees persist in organotypic slice cultures where glucocorticoid levels are irrelevant (Chen et al., 2006b). Thus, CRF_1 receptor may be involved in dendritic differentiation, perhaps pruining related to establishment or maintenance of synapses. The location of this receptor on dendritic spines, directly in the postsynaptic density supports this putative role of the receptor (Chen et al., 2004a,b).

2. CRF_2 receptor: the only information available to the authors about development-specific functions of this receptor is the curious early onset of its expression in ventromedial hypothalamus (see above). Much remains to be studied about the function of these prenatal CRF_2 receptors in the developing hypothalamus.

7. General conclusions

CRH is a key contributor to the repertoire of factors regulating the mammalian response to stress, complementing the actions of glucocorticoids and sympathetic neurotransmitters. In the spatial domain, because the peptide is released from local neurons, it can mediate rapidly the effects of acute stress on specific neuronal populations. Thus, local CRH release in amygdala (Roozendaal et al., 2002) or hippocampus (Chen et al., 2004b, 2006a) can activate selected neuronal populations that carry CRF receptors. In the temporal domain, being a neuropeptide, CRH acts within seconds and exert effects over minutes-to hours, bridging the actions of neurotransmitters (seconds to minutes) and hormones (generally several hours). As highlighted in the current chapter, the central CRH system is very active early in life. During this period, altered regulation of CRH expression levels by early life experiences (handling, chronic early life stress) may last for the duration of the animal's life. Indeed, CRH gene regulation, likely epigenetic, constitutes a major molecular cascade for the long-lasting neuroplasticity of stress response reactivity and cognitive and emotional function later in life.

Reference List

Agid O, Kohn Y, Lerer B. Environmental stress and psychiatric illness. Biomed. Pharmacother 2000;54:135–141. [PubMed: 10840590]

Akana SF, Dallman MF, Bradbury MJ, Scribner KA, Strack AM, Walker CD. Feedback and facilitation in the adrenocortical system: unmasking facilitation by partial inhibition of the glucocorticoid response to prior stress. Endocrinology 1992;131:57–68. [PubMed: 1319329]

Akana SF, Dallman MF. Chronic cold in adrenalectomized, corticosterone (B)-treated rats: facilitated corticotropin responses to acute restraint emerge as B increases. Endocrinology 1997;138:3249–3258. [PubMed: 9231775]

Aldenhoff JB, Gruol DL, Rivier J, Vale W, Siggins GR. Corticotropin releasing factor decreases postburst hyperpolarizations and excites hippocampal neurons. Science 1983;221:875–877. [PubMed: 6603658]

Altman J, Bayer SA. The development of the rat hypothalamus. Adv. Anat. Embryol. Cell. Biol 1986;100:1–178. [PubMed: 3788679]

Anderson SM, Kant GJ, De Souza EB. Effects of chronic stress on anterior pituitary and brain corticotropin-releasing factor receptors. Pharmacol. Biochem. Behav 1993;44:755–761. [PubMed: 8385781]

Arborelius L, Owens MJ, Plotsky PM, Nemeroff CB. The role of corticotropin-releasing factor in depression and anxiety disorders. J. Endocrinol 1999;160:1–12. [PubMed: 9854171]

Avishai-Eliner S, Yi SJ, Newth CJ, Baram TZ. Effects of maternal and sibling deprivation on basal and stress induced hypothalamic-pituitary-adrenal components in the infant rat. Neurosci. Lett 1995;192:49–52. [PubMed: 7675308]

Avishai-Eliner S, Yi SJ, Baram TZ. Developmental profile of messenger RNA for the corticotropin-releasing hormone receptor in the rat limbic system. Dev. Brain. Res 1996;91:159–163. [PubMed: 8852365]

Avishai-Eliner S, Eghbal-Ahmadi M, Tabachnik E, Brunson KL, Baram TZ. Down-regulation of hypothalamic corticotropin-releasing hormone messenger ribonucleic acid (mRNA) precedes early-life experience-induced changes in hippocampal glucocorticoid receptor mRNA. Endocrinology 2001a;142:89–97. [PubMed: 11145570]

Avishai-Eliner S, Gilles EE, Eghbal-Ahmadi M, Bar-El Y, Baram TZ. Altered regulation of gene and protein expression of hypothalamic-pituitary-adrenal axis components in an immature rat model of chronic stress. J. Neuroendocrinol 2001b;13:799–807. [PubMed: 11578530]

Avishai-Eliner S, Brunson KL, Sandman CA, Baram TZ. Stressed-out, or in (utero)? Trends Neurosci 2002;25:518–524. [PubMed: 12220880]

Bale TL, Contarino A, Smith GW, Chan R, Gold LH, Sawchenko PE, Koob GF, Vale WW, Lee KF. Mice deficient for corticotropin-releasing hormone receptor-2 display anxiety-like behaviour and are hypersensitive to stress. Nat. Genet 2000;24:410–414. [PubMed: 10742108]

Baram TZ, Hatalski CG. Neuropeptide-mediated excitability: a key triggering mechanism for seizure generation in the developing brain. Trends Neurosci 1998;21:471–476. [PubMed: 9829688]

Baram TZ, Lerner SP. Ontogeny of corticotropin releasing hormone gene expression in rat hypothalamus--comparison with somatostatin. Int. J. Dev. Neurosci 1991;9:473–478. [PubMed: 1685845]

Baram TZ, Schultz L. Fetal and maternal levels of corticosterone and ACTH after pharmacological adrenalectomy. Life Sci 1990;47:485–489. [PubMed: 2169559]

Baram TZ, Schultz L. CRH gene expression in the fetal rat is not increased after pharmacological adrenalectomy. Neurosci. Lett 1992;142:215–218. [PubMed: 1333578]

Baram TZ, Hirsch E, Snead OC 3rd, Schultz L. Corticotropin-releasing hormone-induced seizures in infant rats originate in the amygdala. Ann. Neurol 1992;31:488–494. [PubMed: 1596084]

Baram TZ, Yi S, Avishai-Eliner S, Schultz L. Development neurobiology of the stress response: multilevel regulation of corticotropin-releasing hormone function. Ann. N. Y. Acad. Sci 1997;814:252–265. [PubMed: 9160975]

Behan DP, Heinrichs SC, Troncoso JC, Liu XJ, Kawas CH, Ling N, De Souza EB. Displacement of corticotropin releasing factor from its binding protein as a possible treatment for Alzheimer's disease. Nature 1995;378:233–234. [PubMed: 7477335]

Bhatnagar S, Dallman M. Neuroanatomical basis for facilitation of hypothalamic-pituitary-adrenal responses to a novel stressor after chronic stress. Neuroscience 1998;84:1025–1039. [PubMed: 9578393]

Blank T, Nijholt I, Eckart K, Spiess J. Priming of long-term potentiation in mouse hippocampus by corticotropin-releasing factor and acute stress: implications for hippocampus-dependent learning. J. Neurosci 2002;22:3788–3794. [PubMed: 11978854]

Blank T, Nijholt I, Grammatopoulos DK, Randeva HS, Hillhouse EW, Spiess J. Corticotropin-releasing factor receptors couple to multiple G-proteins to activate diverse intracellular signaling pathways in mouse hippocampus: role in neuronal excitability and associative learning. J. Neurosci 2003;23:700–707. [PubMed: 12533630]

Bonaz B, Rivest S. Effect of a chronic stress on CRF neuronal activity and expression of its type 1 receptor in the rat brain. Am J Physiol 1998;275:1438–1449.

Brown CP, Smotherman WP, Levine S. Interaction-induced reduction in differential maternal responsiveness: an effect of cue-reduction or behavior? Dev. Psychobiol 1977;10:273–280. [PubMed: 863123]

Brunson KL, Avishai-Eliner S, Hatalski CG, Baram TZ. Neurobiology of the stress response early in life: evolution of a concept and the role of corticotrophin releasing hormone. Mol. Psychiatry 2001a; 6:647–656. [PubMed: 11673792]

Brunson KL, Eghbal-Ahmadi M, Bender R, Chen Y, Baram TZ. Long-term, progressive hippocampal cell loss and dysfunction induced by early-life administration of corticotropin-releasing hormone reproduce the effects of early-life stress. Proc. Natl. Acad. Sci. U. S. A 2001b;98:8856–8861. [PubMed: 11447269]

Brunson KL, Grigoriadis DE, Lorang MT, Baram TZ. Corticotropin-releasing hormone (CRH) downregulates the function of its receptor (CRF1) and induces CRF1 expression in hippocampal and cortical regions of the immature rat brain. Exp. Neurol 2002;176:75–86. [PubMed: 12093084]

Brunson KL, Kramar E, Lin B, Chen Y, Colgin LL, Yanagihara TK, Lynch G, Baram TZ. Mechanisms of late-onset cognitive decline after early-life stress. J. Neurosci 2005;25:9328–9338. [PubMed: 16221841]

Bugnon C, Fellmann D, Gouget A, Cardot J. Ontogeny of the corticoliberin neuroglandular system in rat brain. Nature 1982;298:159–161. [PubMed: 6979719]

Caldji C, Tannenbaum B, Sharma S, Francis D, Plotsky PM, Meaney MJ. Maternal care during infancy regulates the development of neural systems mediating the expression of fearfulness in the rat. Proc. Natl. Acad. Sci. U. S. A 1998;95:5335–5340. [PubMed: 9560276]

Calogero AE, Liapi C, Chrousos GP. Hypothalamic and suprahypothalamic effects of prolonged treatment with dexamethasone in the rat. J. Endocrinol. Invest 1991;14:277–286. [PubMed: 1650804]

Chalmers DT, Lovenberg TW, De Souza EB. Localization of novel corticotropin-releasing factor receptor (CRF2) mRNA expression to specific subcortical nuclei in rat brain: comparison with CRF1 receptor mRNA expression. J. Neurosci 1995;15:6340–6350. [PubMed: 7472399]

Charney DS, Manji HK. Life stress, genes, and depression: multiple pathways lead to increased risk and new opportunities for intervention. Sci. STKE 2004:16.

Chen Y, Brunson KL, Muller MB, Cariaga W, Baram TZ. Immunocytochemical distribution of corticotropin-releasing hormone receptor type-1 (CRF(1))-like immunoreactivity in the mouse brain: light microscopy analysis using an antibody directed against the C-terminus. J. Comp. Neurol 2000;420:305–323. [PubMed: 10754504]

Chen Y, Bender RA, Frotscher M, Baram TZ. Novel and transient populations of corticotropin-releasing hormone-expressing neurons in developing hippocampus suggest unique functional roles: a quantitative spatiotemporal analysis. J. Neurosci 2001a;21:7171–7181. [PubMed: 11549728]

Chen Y, Hatalski CG, Brunson KL, Baram TZ. Rapid phosphorylation of the CRE binding protein precedes stress-induced activation of the corticotropin releasing hormone gene in medial parvocellular hypothalamic neurons of the immature rat. Mol. Brain Res 2001b;96:39–49. [PubMed: 11731007]

Chen Y, Bender RA, Brunson KL, Pomper JK, Grigoriadis DE, Wurst W, Baram TZ. Modulation of dendritic differentiation by corticotropin-releasing factor in the developing hippocampus. Proc. Natl. Acad. Sci. U. S. A 2004a;101:15782–15787. [PubMed: 15496472]

Chen Y, Brunson KL, Adelmann G, Bender RA, Frotscher M, Baram TZ. Hippocampal corticotropin releasing hormone: pre- and postsynaptic location and release by stress. Neuroscience 2004b; 126:533–540. [PubMed: 15183503]

Chen Y, Fenoglio KA, Dube CM, Grigoriadis DE, Baram TZ. Cellular and molecular mechanisms of hippocampal activation by acute stress are age-dependent. Mol. Psychiatry 2006a;11:992–1002. [PubMed: 16801951]

Chen Y, Patel NA, Dube C, Burgdorff CJ, Baram TZ. Dendritic branching and spine density in developing hippocampus are governed by corticotropin-releasing hormone receptors: implications for early-life stress. Abstarct Soc. for Neuroscience 2006b:n. 357.8/AA29.

Coste SC, Kesterson RA, Heldwein KA, Stevens SL, Heard AD, Hollis JH, Murray SE, Hill JK, Pantely GA, Hohimer AR, Hatton DC, Phillips TJ, Finn DA, Low MJ, Rittenberg MB, Stenzel P, Stenzel-

Poore MP. Abnormal adaptations to stress and impaired cardiovascular function in mice lacking corticotropin-releasing hormone receptor-2. Nat. Genet 2000;24:403–409. [PubMed: 10742107]

Coste SC, Murray SE, Stenzel-Poore MP. Animal models of CRH excess and CRH receptor deficiency display altered adaptations to stress. Peptides 2001;22:733–741. [PubMed: 11337086]

Curtis AL, Valentino RJ. Corticotropin-releasing factor neurotransmission in locus coeruleus: a possible site of antidepressant action. Brain Res. Bull 1994;35:581–587. [PubMed: 7859115]

Daikoku, S.; Hisano, S. Development of corticotropin releasing factor in the rat brain. In: Bjorkland, A.; Hokfelt, T.; Tohyama, M., editors. Handbook of Chemical Neuroanatomy. Vol 10. Amsterdam: Elsevier; 1992. p. 477-520.

Dallman MF. Moments in time--the neonatal rat hypothalamo-pituitary-adrenal axis. Endocrinology 2000;141:1590–1592. [PubMed: 10803565]

Dayas CV, Buller KM, Crane JW, Xu Y, Day TA. Stressor categorization: acute physical and psychological stressors elicit distinctive recruitment patterns in the amygdala and in medullary noradrenergic cell groups. Eur. J. Neurosci 2001;14:1143–1152. [PubMed: 11683906]

Deak T, Nguyen KT, Cotter CS, Fleshner M, Watkins LR, Maier SF, Spencer RL. Long-term changes in mineralocorticoid and glucocorticoid receptor occupancy following exposure to an acute stressor. Brain Res 1999;847:211–220. [PubMed: 10575090]

Denenberg VH, Whimby AE. Behavior of adult rats is modified by the experiences their mothers had as infants. Science 1963;142:1192–1193. [PubMed: 14069245]

Dent GW, Smith MA, Levine S. Rapid induction of corticotropin-releasing hormone gene transcription in the paraventricular nucleus of the developing rat. Endocrinology 2000;141:1593–1598. [PubMed: 10803566]

De Souza EB. Corticotropin-releasing factor receptors: physiology, pharmacology, biochemistry and role in central nervous system and immune disorders. Psychoneuroendocrinology 1995;20:789–819. [PubMed: 8834089]

Dunn AJ, Berridge CW. Physiological and behavioral responses to corticotropin-releasing factor administration: is CRF a mediator of anxiety or stress responses? Brain Res Rev 1990;15:71–100. [PubMed: 1980834]

Eghbal-Ahmadi M, Hatalski CG, Avishai-Eliner S, Baram TZ. Corticotropin releasing factor receptor type II (CRF2) messenger ribonucleic acid levels in the hypothalamic ventromedial nucleus of the infant rat are reduced by maternal deprivation. Endocrinology 1997;138:5048–5051. [PubMed: 9348237]

Eghbal-Ahmadi M, Hatalski CG, Lovenberg TW, Avishai-Eliner S, Chalmers DT, Baram TZ. The developmental profile of the corticotropin releasing factor receptor (CRF2) in rat brain predicts distinct age-specific functions. Dev. Brain Res 1998;107:81–90. [PubMed: 9602071]

Eghbal-Ahmadi M, Avishai-Eliner S, Hatalski CG, Baram TZ. Differential regulation of the expression of corticotropin-releasing factor receptor type 2 (CRF2) in hypothalamus and amygdala of the immature rat by sensory input and food intake. J. Neurosci 1999;19:3982–3991. [PubMed: 10234028]

Ehlers CL, Henriksen SJ, Wang M, Rivier J, Vale W, Bloom FE. Corticotropin releasing factor produces increases in brain excitability and convulsive seizures in rats. Brain Res 1983;278:332–336. [PubMed: 6605787]

Fenoglio KA, Brunson KL, Avishai-Eliner S, Chen Y, Baram TZ. Region-specific onset of handling-induced changes in corticotropin-releasing factor and glucocorticoid receptor expression. Endocrinology 2004;145:2702–2706. [PubMed: 15044366]

Fenoglio KA, Brunson KL, Baram TZ. Hippocampal neuroplasticity induced by early-life stress: functional and molecular aspects. Front. Neuroendocrinol 2006a;27:180–192. [PubMed: 16603235]

Fenoglio KA, Chen Y, Baram TZ. Neuroplasticity of the hypothalamic-pituitary-adrenal axis early in life requires recurrent recruitment of stress-regulating brain regions. J. Neurosci 2006b;26:2434–2442. [PubMed: 16510721]

Francis DD, Caldji C, Champagne F, Plotsky PM, Meaney MJ. The role of corticotropin-releasing factor--norepinephrine systems in mediating the effects of early experience on the development of behavioral and endocrine responses to stress. Biol. Psychiatry 1999;46:1153–1166. [PubMed: 10560022]

Gilles EE, Schultz L, Baram TZ. Abnormal corticosterone regulation in an immature rat model of continuous chronic stress. Pediatr. Neurol 1996;15:114–119. [PubMed: 8888044]

Gonzalez GA, Montminy MR. Cyclic AMP stimulates somatostatin gene transcription by phosphorylation of CREB at serine 133. Cell 1989;59:675–680. [PubMed: 2573431]

Gray TS, Bingaman EW. The amygdala: corticotropin-releasing factor, steroids, and stress. Crit. Rev. Neurobiol 1996;10:155–168. [PubMed: 8971127]

Grino M, Young WS 3rd, Burgunder JM. Ontogeny of expression of the corticotropin-releasing factor gene in the hypothalamic paraventricular nucleus and of the proopiomelanocortin gene in rat pituitary. Endocrinology 1989;124:60–68. [PubMed: 2783310]

Hatalski CG, Guirguis C, Baram TZ. Corticotropin releasing factor mRNA expression in the hypothalamic paraventricular nucleus and the central nucleus of the amygdala is modulated by repeated acute stress in the immature rat. J. Neuroendocrinol 1998;10:663–669. [PubMed: 9744483]

Hatalski CG, Brunson KL, Tantayanubutr B, Chen Y, Baram TZ. Neuronal activity and stress differentially regulate hippocampal and hypothalamic corticotropin-releasing hormone expression in the immature rat. Neuroscience 2000;101:571–580. [PubMed: 11113306]

Harbuz MS, Lightman SL. Responses of hypothalamic and pituitary mRNA to physical and psychological stress in the rat. J. Endocrinol 1989;122:705–711. [PubMed: 2809478]

Harbuz MS, Rees RG, Eckland D, Jessop DS, Brewerton D, Lightman SL. Paradoxical responses of hypothalamic corticotropin-releasing factor (CRF) messenger ribonucleic acid (mRNA) and CRF-41 peptide and adenohypophysial proopiomelanocortin mRNA during chronic inflammatory stress. Endocrinology 1992;130:1394–1400. [PubMed: 1537299]

Hauger RL, Millan MA, Lorang M, Harwood JP, Aguilera G. Corticotropin-releasing factor receptors and pituitary adrenal responses during immobilization stress. Endocrinology 1988;123:396–405. [PubMed: 2838259]

Herman JP, Cullinan WE. Neurocircuitry of stress: central control of the hypothalamo-pituitary-adrenocortical axis. Trends Neurosci 1997;20:78–84. [PubMed: 9023876]

Herman JP, Schafer MK, Young EA, Thompson R, Douglass J, Akil H, Watson SJ. Evidence for hippocampal regulation of neuroendocrine neurons of the hypothalamo-pituitary-adrenocortical axis. J. Neurosci 1989;9:3072–3082. [PubMed: 2795152]

Herman JP, Ostrander MM, Mueller NK, Figueiredo H. Limbic system mechanisms of stress regulation: hypothalamo-pituitary-adrenocortical axis. Prog. Neuropsychopharmacol. Biol. Psychiatry 2005;29:1201–1213. [PubMed: 16271821]

Herringa RJ, Mackenrodt DB, Barlow JD, Roseboom PH, Nanda SA, Kalin NH. Corticotropin-releasing factor (CRF), but not corticosterone, increases basolateral amygdala CRF-binding protein. Brain Res 2006;1083:21–28. [PubMed: 16545343]

Hollrigel GS, Chen K, Baram TZ, Soltesz I. The pro-convulsant actions of corticotropin-releasing hormone in the hippocampus of infant rats. Neuroscience 1998;84:71–79. [PubMed: 9522363]

Holsboer F, Barden N. Antidepressants and hypothalamic-pituitary-adrenocortical regulation. Endocr. Rev 1996;17:187–205. [PubMed: 8706631]

Imaki T, Nahan JL, Rivier C, Sawchenko PE, Vale W. Differential regulation of corticotropin-releasing factor mRNA in rat brain regions by glucocorticoids and stress. J. Neurosci 1991;11:585–599. [PubMed: 2002354]

Imaki T, Naruse M, Harada S, Chikada N, Imaki J, Onodera H, Demura H, Vale W. Corticotropin-releasing factor up-regulates its own receptor mRNA in the paraventricular nucleus of the hypothalamus. Mol. Brain Res 1996;38:166–170. [PubMed: 8737681]

Imaki T, Katsumata H, Miyata M, Naruse M, Imaki J, Minami S. Expression of corticotropin-releasing hormone type 1 receptor in paraventricular nucleus after acute stress. Neuroendocrinology 2001;73:293–301. [PubMed: 11399902]

Imaki T, Katsumata H, Konishi SI, Kasagi Y, Minami S. Corticotropin-releasing factor type-1 receptor mRNA is not induced in mouse hypothalamus by either stress or osmotic stimulation. J. Neuroendocrinol 2003;15:916–924. [PubMed: 12969235]

Iredale PA, Terwilliger R, Widnell KL, Nestle rEJ, Duman RS. Differential regulation of corticotropin-releasing factor1 receptor expression by stress and agonist treatments in brain and cultured cells. Mol. Pharmacol 1996;50:1103–1110. [PubMed: 8913341]

Ixart G, Barbanel G, Conte-Devolx B, Grino M, Oliver C, Assenmacher I. Evidence for basal and stress-induced release of corticotropin releasing factor in the push-pull cannulated median eminence of conscious free-moving rats. Neurosci. Lett 1987;74:85–89. [PubMed: 3031554]

Joels M, Karst H, Alfarez D, Heine VM, Qin Y, van Riel E, Verkuyl M, Lucassen PJ, Krugers HJ. Effects of chronic stress on structure and cell function in rat hippocampus and hypothalamus. Stress 2004;7:221–231. [PubMed: 16019587]

Kalin NH, Takahash iLK, Chen FL. Restraint stress increases corticotropin-releasing hormone mRNA content in the amygdala and paraventricular nucleus. Brain Res 1994;656:182–186. [PubMed: 7804835]

Keegan CE, Herman JP, Karolyi IJ, O'Shea KS, Camper SA, Seasholtz AF. Differential expression of corticotropin-releasing hormone in developing mouse embryos and adult brain. Endocrinology 1994;134:2547–2555. [PubMed: 8194481]

King JS, Madtes P, Bishop GA, Overbeck TL. The distribution of corticotropin-releasing factor (CRF),CRF binding sites and CRF1 receptor mRNA in the mouse cerebellum. Prog. Brain Res 1997;114:55–66. [PubMed: 9193138]

Kirby LG, Rice KC, Valentino RJ. Effects of corticotropin-releasing factor on neuronal activity in the serotonergic dorsal raphe nucleus. Neuropsychopharmacology. Neuropsychopharmacology 2000;22:449.

Kjelstrup KG, Tuvnes FA, Steffenach HA, Murison R, Moser EI, Moser MB. Reduced fear expression after lesions of the ventral hippocampus. Proc. Natl. Acad. Sci. USA 2002;99:10825–10830. [PubMed: 12149439]

Koegler-Muly SM, Owens MJ, Ervin GN, Kilts CD, Nemeroff CB. Potential corticotropin-releasing factor pathways in the rat brain as determined by bilateral electrolytic lesions of the central amygdaloid nucleus and the paraventricular nucleus of the hypothalamus. J. Neuroendocrinol 1993;5:95–98. [PubMed: 8485547]

Koob GF. The neurobiology of addiction: a neuroadaptational view relevant for diagnosis. Addiction 2006;101:23–30. [PubMed: 16930158]

Korosi A, Schotanus S, Olivier B, Roubos EW, Kozicz T. Chronic ether stress-induced response of urocortin 1 neurons in the Edinger-Westphal nucleus in the mouse. Brain Res 2005;1046:172–179. [PubMed: 15885665]

Korosi A, Veening JG, Kozicz T, Henckens M, Dederen J, Groenink L, van der Gugten J, Olivier B, Roubos EW. Distribution and expression of CRF receptor 1 and 2 mRNAs in the CRF over-expressing mouse brain. Brain Res 2006;1072:46–54. [PubMed: 16423327]

Kovacs KJ, Sawchenko PE. Sequence of stress-induced alterations in indices of synaptic and transcriptional activation in parvocellular neurosecretory neurons. J. Neurosci 1996;16:262–273. [PubMed: 8613792]

Kozicz T, Korosi A, Korsman C, Tilburg-Ouwens D, Groenink L, Veening J, van Der Gugten J, Roubos E, Olivier B. Urocortin expression in the Edinger-Westphal nucleus is down-regulated in transgenic mice over-expressing neuronal corticotropin-releasing factor. Neuroscience 2004;123:589–594. [PubMed: 14706771]

Levine S. Infantile experience and resistance to physiological stress. Science 1957;126:405. [PubMed: 13467220]

Levine S. Maternal and environmental influences on the adrenocortical response to stress in weanling rats. Science 1967;156:258–260. [PubMed: 6021047]

Levine S. The pituitary-adrenal system and the developing brain. Prog. Brain Res 1970;32:79–85. [PubMed: 4322026]

Levine S. The ontogeny of the hypothalamic-pituitary-adrenal axis. The influence of maternal factors. Ann. N. Y. Acad. Sci 1994;746:275–288. [PubMed: 7825883]

Lightman SL, Harbuz MS. Expression of corticotropin-releasing factor mRNA in response to stress. Ciba. Found. Symp 1993;172:173–187. [PubMed: 8491086]

Lightman SL, Young WS. Influence of steroids on the hypothalamic corticotropin-releasing factor and preproenkephalin mRNA responses to stress. Proc. Natl. Acad. Sci. USA 1989;86:4306–4310. [PubMed: 2786213]

Liu D, Diorio J, Tannenbaum B, Caldji C, Francis D, Freedman A, Sharma S, Pearson D, Plotsky PM, Meaney MJ. Maternal care, hippocampal glucocorticoid receptors, and hypothalamic-pituitary-adrenal responses to stress. Science 1997;277:1659–1662. [PubMed: 9287218]

Lovenberg TW, Liaw CW, Grigoriadis DE, Clevenger W, Chalmers DT, De Souza EB, Oltersdorf T. Cloning and characterization of a functionally distinct corticotropin-releasing factor receptor subtype from rat brain. Proc. Natl. Acad. Sci. USA 1995;92:836–840. [PubMed: 7846062]

Luo X, Kiss A, Makara G, Lolait SJ, Aguilera G. Stress-specific regulation of corticotropin releasing hormone receptor expression in the paraventricular and supraoptic nuclei of the hypothalamus in the rat. J. Neuroendocrinol 1994;6:689–696. [PubMed: 7894472]

Makino S, Gold PW, Schulkin J. Corticosterone effects on corticotropin-releasing hormone mRNA in the central nucleus of the amygdala and the parvocellular region of the paraventricular nucleus of the hypothalamus. Brain Res 1994;640:105–112. [PubMed: 8004437]

Makino S, Schulkin J, Smith MA, Pacak K, Palkovits M, Gold PW. Regulation of corticotropin-releasing hormone receptor messenger ribonucleic acid in the rat brain and pituitary by glucocorticoids and stress. Endocrinology 1995a;136:4517–4525. [PubMed: 7664672]

Makino S, Smith MA, Gold PW. Increased expression of corticotropin-releasing hormone and vasopressin messenger ribonucleic acid (mRNA) in the hypothalamic paraventricular nucleus during repeated stress: association with reduction in glucocorticoid receptor mRNA levels. Endocrinology 1995b;136:3299–3309. [PubMed: 7628364]

Makino S, Takemura T, Asaba K, Nishiyama M, Takao T, Hashimoto K. Differential regulation of type-1 and type-2alpha corticotropin-releasing hormone receptor mRNA in the hypothalamic paraventricular nucleus of the rat. Mol. Brain Res 1997;47:170–176. [PubMed: 9221914]

Makino S, Nishiyama M, Asaba K, Gold PW, Hashimoto K. Altered expression of type 2 CRH receptor mRNA in the VMH by glucocorticoids and starvation. Am. J. Physiol 1998;275:1138–1145.

Mansi JA, Rivest S, Drolet G. Regulation of corticotropin-releasing factor type 1 (CRF1) receptor messengerribonucleic acid in the paraventricular nucleus of rat hypothalamus by exogenous CRF. Endocrinology 1996;137:4619–4629. [PubMed: 8895325]

Marrosu F, Fratta W, Carcangiu P, Giagheddu M, Gessa GL. Localized epileptiform activity induced by murine CRF in rats. Epilepsia 1988;29:369–373. [PubMed: 3260555]

McEwen BS, Milner TA. Hippocampal formation: Shedding light on the influence of sex and stress on the brain. Brain Res. Rev. 2007Epub ahead of print

McGaugh JL, Cahill L, Roozendaal B. Involvement of the amygdala in memory storage: interaction with other brain systems. Proc. Natl. Acad. Sci. USA 1996;93:13508–12514. [PubMed: 8942964]

McKnight GS, Clegg CH, Uhler MD, Chrivia JC, Cadd GG, Correll LA, Otten AD. Analysis of the cAMP-dependent protein kinase system using molecular genetic approaches. Recent Prog. Horm. Res 1988;44:307–335. [PubMed: 3217600]

Meijer OC, de Kloet ER. Corticosterone and serotonergic neurotransmission in the hippocampus: functional implications of central corticosteroid receptor diversity. Crit. Rev. Neurobiol 1998;12:1–20. [PubMed: 9444479]

Merali Z, McIntosh J, Kent P, Michaud D, Anisman H. Aversive and appetitive events evoke the release of corticotropin-releasing hormone and bombesin-like peptides at the central nucleus of the amygdala. J. Neurosci 1998;18:4758–4766. [PubMed: 9614249]

Merali Z, Khan S, Michaud DS, Shippy SA, Anisman H. Does amygdaloid corticotropin-releasing hormone (CRH) mediate anxiety-like behaviors? Dissociation of anxiogenic effects and CRH release. Eur. J. Neurosci 2004;20:229–239. [PubMed: 15245495]

Merchenthaler I. Corticotropin releasing factor (CRF)-like immunoreactivity in the rat central nervous system. Extrahypothalamic distribution. Peptides 1984;5:53–69. [PubMed: 6384954]

Merchenthaler I, Vigh S, Petrusz P, Schally AV. Immunocytochemical localization of corticotropin-releasing factor (CRF) in the rat brain. Am. J. Anat 1982;165:385–396. [PubMed: 6760710]

Morin SM, Ling N, Liu XJ, Kahl SD, Gehlert DR. Differential distribution of urocortin- and corticotropin-releasing factor-like immunoreactivities in the rat brain. Neuroscience 1999;92:281–291. [PubMed: 10392850]

Nemeroff CB. Early-Life Adversity, CRF Dysregulation, and Vulnerability to Mood and Anxiety Disorders. Psychopharmacol. Bull 2004;38:14–20. [PubMed: 17065965]

Nemeroff CB, Vale WW. The neurobiology of depression: inroads to treatment and new drug discovery. J. Clin. Psychiatry 2005;7:5–13. [PubMed: 16124836]

Owens MJ, Nemeroff CB. Physiology and pharmacology of corticotropin-releasing factor. Pharmacol. Rev 1991;43:425–473. [PubMed: 1775506]

Palkovits M, Young WS, Kovacs K, Toth Z, Makara GB. Alterations in corticotropin-releasing hormone gene expression of central amygdaloid neurons following long-term paraventricular lesions and adrenalectomy. Neuroscience 1998;85:135–147. [PubMed: 9607709]

Perrin MH, Donaldson CJ, Chen R, Lewis KA, Vale WW. Cloning and functional expression of a rat brain corticotropin releasing factor(CRF) receptor. Endocrinology 1993;133:3058–3061. [PubMed: 8243338]

Potter E, Sutton S, Donaldson C, Chen R, Perrin M, Lewis K, Sawchenko PE, Vale W. Distribution of corticotropin-releasing factor receptor mRNA expression in the rat brain and pituitary. Proc. Natl. Acad. Sci. USA 1994;91:8777–8781. [PubMed: 8090722]

Plotsky PM, Meaney MJ. Early, postnatal experience alters hypothalamic corticotropin-releasing factor (CRF) mRNA, median eminence CRF content and stress-induced release in adult rats. Mol. Brain Res 1993;18:195–200. [PubMed: 8497182]

Plotsky PM, Sawchenko PE. Hypophysial-portal plasma levels, median eminence content, and immunohistochemical staining of corticotropin-releasing factor, arginine vasopressin, and oxytocin after pharmacological adrenalectomy. Endocrinology 1987;120:1361–1369. [PubMed: 3030697]

Plotsky PM, Thrivikraman KV, Nemeroff CB, Caldji C, Sharma S, Meaney MJ. Long-term consequences of neonatal rearing on central corticotropin-releasing factor systems in adult male rat offspring. Neuropsychopharmacology 2005;30:2192–2204. [PubMed: 15920504]

Rehman HU. Role of CRH in the pathogenesis of dementia of Alzheimer's type and other dementias. Curr. Opin. Investig. Drugs 2002;3:1637–1642.

Reul JM, Holsboer F. Corticotropin-releasing factor receptors 1 and 2 in anxiety and depression. Curr. Opin. Pharmacol 2002;2:23–33. [PubMed: 11786305]

Rivest S, Laflamme N, Nappi RE. Immune challenge and immobilization stress induce transcription of the gene encoding the CRF receptor in selective nuclei of the rat hypothalamus. J. Neurosci 1995;15:2680–2695. [PubMed: 7722622]

Roozendaal B, Koolhaas JM, Bohus B. The role of the central amygdala in stress and adaption. Acta Physiol. Scand 1997;640:51–54.

Roozendaal B, Sapolsky RM, McGaugh JL. Basolateral amygdala lesions block the disruptive effects of long-term adrenalectomy on spatial memory. Neuroscience 1998;84:453–465. [PubMed: 9539216]

Roozendaal B, Brunson KL, Holloway BL, McGaugh JL, Baram TZ. Involvement of stress-released corticotropin-releasing hormone in the basolateral amygdala in regulating memory consolidation. Proc. Natl. Acad. Sci. U. S. A 2002;99:13908–13913. [PubMed: 12361983]

Rossant CJ, Pinnock RD, Hughes J, Hall MD, McNulty S. Corticotropin-releasing factor type 1 and type 2alpha receptors regulate phosphorylation of calcium/cyclic adenosine 3′,5′-monophosphate response element-binding protein and activation of p42/p44 mitogen-activated protein kinase. Endocrinology 1999;140:1525–1536. [PubMed: 10098484]

Sakanaka M, Shibasaki T, Lederis K. Corticotropin releasing factor-like immunoreactivity in the rat brain as revealed by a modified cobalt-glucose oxidase-diaminobenzidine method. J. Comp. Neurol 1987;260:256–298. [PubMed: 3497182]

Sanchez MM, Ladd CO, Plotsky PM. Early adverse experience as a developmental risk factor for later psychopathology: evidence from rodent and primate models. Dev. Psychopathol 2001;13:419–449. [PubMed: 11523842]

Sawchenko PE, Swanson LW. Localization, colocalization, and plasticity of corticotropin-releasing factor immunoreactivity in rat brain. Fed. Proc 1985;44:221–227. [PubMed: 2981743]

Schmidt M, Enthoven L, van Woezik JH, Levine S, de Kloet ER, Oitzl MS. The dynamics of the hypothalamic-pituitary-adrenal axis during maternal deprivation. J. Neuroendocrinol 2004;16:52–57. [PubMed: 14962076]

Schmidt MV, Oitzl MS, Muller MB, Ohl F, Wurst W, Holsboer F, Levine S, De Kloet ER. Regulation of the developing hypothalamic-pituitary-adrenal axis in corticotropin releasing hormone receptor 1-deficient mice. Neuroscience 2003;119:589-55. [PubMed: 12770571]

Schmidt MV, Deussing JM, Oitzl MS, Ohl F, Levine S, Wurst W, Holsboer F, Muller MB, de Kloet ER. Differential disinhibition of the neonatal hypothalamic-pituitary-adrenal axis in brain-specific CRH receptor 1-knockout mice. Eur. J. Neurosci 2006;24:2291–2298. [PubMed: 17042789]

Smith MA, Kim SY, van Oers HJ, Levine S. Maternal deprivation and stress induce immediate early genes in the infant rat brain. Endocrinology 1997a;138:4622–4628. [PubMed: 9348187]

Smith MA, Weiss SR, Berry RL, Zhang LX, Clark M, Massenburg G, Post RM. Amygdala-kindled seizures increase the expression of corticotropin-releasing factor (CRF) and CRF-binding protein in GABAergic interneurons of the dentatehilus. Brain Res 1997b;745:248–256. [PubMed: 9037416]

Swanson LW, Simmons DM. Differential steroid hormone and neural influences on peptide mRNA levels in CRH cells of the paraventricular nucleus: a hybridization histochemical study in the rat. J. Comp. Neurol 1989;285:413–435. [PubMed: 2569487]

Swanson LW, Sawchenko PE, Rivier J, Vale WW. Organization of ovine corticotropin-releasing factor immunoreactive cells and fibers in the rat brain: an immunohistochemical study. Neuroendocrinology 1983;36:165–186. [PubMed: 6601247]

Timofeeva E, Richard D. Functional activation of CRH neurons and expression of the genes encoding CRH and its receptors in food-deprived lean (Fa/?) and obese (fa/fa) Zucker rats. Neuroendocrinology 1997;66:327–340. [PubMed: 9387852]

Vale W, Spiess J, Rivier C, Rivier J. Characterization of a 41-residue ovine hypothalamic peptide that stimulates secretion of corticotropin and beta-endorphin. Science 1981;213:1394–1397. [PubMed: 6267699]

Van Bockstaele EJ, Colago EE, Valentino RJ. Corticotropin-releasing factor-containing axon terminals synapse onto catecholamine dendrites and may presynaptically modulate other afferents in the rostral pole of the nucleus locus coeruleus in the rat brain. J. Comp. Neurol 1996;364:523–534. [PubMed: 8820881]

van Oers HJ, de Kloet ER, Whelan T, Levine S. Maternal deprivation effect on the infant's neural stress markers is reversed by tactile stimulation and feeding but not by suppressing corticosterone. J. Neurosci 1998;18:10171–10179. [PubMed: 9822770]

van Oers HJ, de Kloet ER, Levine S. Persistent effects of maternal deprivation on HPA regulation can be reversed by feeding and stroking, but not by dexamethasone. J. Neuroendocrinol 1999;11:581–588. [PubMed: 10447795]

Van Pett K, Viau V, Bittencourt JC, Chan RK, Li HY, Arias C, Prins GS, Perrin M, Vale W, Sawchenko PE. Distribution of mRNAs encoding CRF receptors in brain and pituitary of rat and mouse. J. Comp. Neurol 2000;428:191–212. [PubMed: 11064361]

Vaughan J, Donaldson C, Bittencourt J, Perrin MH, Lewis K, Sutton S, Chan R, Turnbull AV, Lovejoy D, Rivier C. Urocortin, a mammalian neuropeptide related to fish urotensin I and to corticotropin-releasing factor. Nature 1995;378:287–292. [PubMed: 7477349]

Vazquez DM. Stress and the developing limbic-hypothalamic-pituitary-adrenal axis. Psychoneuroendocrinology 1998;23:663–700. [PubMed: 9854741]

Vazquez DM, Bailey C, Dent GW, Okimoto DK, Steffek A, Lopez JF, Levine S. brain corticotropin-releasing hormone (CRH) circuits in the developing rat:effect of maternal deprivation. Brain Res 2006;1121:83–94. [PubMed: 17055465]

Walker CD, Dallman MF. Neonatal facilitation of stress-induced adrenocorticotropin secretion by prior stress: evidence for increased central drive to the pituitary. Endocrinology 1993;132:1101–1107. [PubMed: 8382596]

Wang HL, Wayner MJ, Chai CY, Lee EH. Corticotrophin-releasing factor produces a long-lasting enhancement of synaptic efficacy in the hippocampus. Eur. J. Neurosci 1998;10:3428–3437. [PubMed: 9824456]

Welberg LA, Seckl JR. Prenatal stress, glucocorticoids and the programming of the brain. J. Neuroendocrinol 2001;13:113–128. [PubMed: 11168837]

Yan XX, Toth Z, Schultz L, Ribak CE, Baram TZ. Corticotropin-releasing hormone (CRH)-containing neurons in the immature rat hippocampal formation: light and electron microscopic features and colocalization with glutamate decarboxylase and parvalbumin. Hippocampus 1998;8:231–243. [PubMed: 9662138]

Yi SJ, Baram TZ. Methods for implanting steroid-containing cannulae into the paraventricular nucleus of neonatal rats. J. Pharmacol. Toxicol. Methods 1993;30:97–102. [PubMed: 8298186]

Yi SJ, Baram TZ. Corticotropin-releasing hormone mediates the response to cold stress in the neonatal rat without compensatory enhancement of the peptide's gene expression. Endocrinology 1994;135:2364–2368. [PubMed: 7988418]

Yi SJ, Masters JN, Baram TZ. Effects of a specific glucocorticoid receptor antagonist on corticotropin releasing hormone gene expression in the paraventricular nucleus of the neonatal rat. Dev. Brain Res 1993;73:253–259. [PubMed: 8353935]

Yi SJ, Masters JN, Baram TZ. Glucocorticoid receptor mRNA ontogeny in the fetal and postnatal rat forebrain. Mol. Cell. Neurosci 1994;5:385–393. [PubMed: 7820362]