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Stress Neurobiology and Corticotropin-Releasing Factor

David A. Gutman, MD, PhD, Alisa R. Gutman, Michael J. Owens, PhD, and Charles B. Nemeroff, MD, PhD

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Educational Objectives:
After reading this article, you will be familiar with:

- The evidence linking hypothalamicpituitary- adrenal axis abnormalities and psychiatric symptoms.
- The role of corticotropin-releasing factor (CRF) in depressed patients.
- Extrahypothalamic CRF circuits and their impact on depression.

Who will benefit from reading this article?

Psychiatrists, primary care physicians, neurologists, nurse practitioners, psychiatric nurses, and other mental health care professionals. Continuing medical education credit is available for most specialties. To determine whether this article meets the CE requirements for your specialty, please contact your state licensing board.

Dr Gutman is a resident in the department of psychiatry; Ms Gutman is an MD, PhD candidate; Dr Owens is associate professor in the department of psychiatry and behavioral sciences and associate director of the laboratory of neuropsychopharmacology; and Dr Nemeroff is Reunette W. Harris Professor and chair of the department of psychiatry and behavioral sciences at Emory University School of Medicine in Atlanta.

The concept that stressful life events may render one vulnerable to psychiatric disease has been a mainstay of the psychiatric literature for more than a century. This idea was initiated, in part, by the pioneering work of Sigmund Freud,who used psychoanalytic methods to explore the relationship between stressful life events and psychopathology. These concepts slowly evolved into more biologically based theories with the early work of Hans Selye, who studied the relationshipbetween stress, illness, and emotions. The occurrence of depression, anxiety, and other psychiatric symptoms in both Cushing and Addison diseases, which are associated with excessive or markedly reduced levels of circulating glucocorticoids, respectively, served as a further impetus for researchers to scrutinize hypothalamic-pituitary-adrenal (HPA) axis function in psychiatric disorders.

HPA axis abnormalities in depression

Evidence linking HPA axis abnormalities and psychiatric symptoms dates back over 100 years, and numerous studies have been conducted in this area. Some of the earliest controlled clinical studies in psychiatry, dating back to the 1950s, demonstrated a number of abnormalities in glucocorticoid (ie, cortisol) function in depressed patients, including elevated plasma cortisol concentrations,[1,2] increased 24-hour urinary free cortisol concentrations, and increased levels of cortisol metabolites in urine.[3] Elevated cortisol secretion in depression is among the most reproducible findings in all of biologic psychiatry.

Structural changes in the components of the HPA axis have also been documented in depressed patients, including pituitary gland enlargement demonstrated by MRI[4] and enlargement of the adrenal glands, presumably due to adrenocorticotropic hormone (ACTH) hypersecretion in depressed patients postmortem[5,6] and in suicide victims.[7] The adrenal gland enlargement seen in depression has been confirmed using MRI, and it appears to be state-dependent,[8,9] waxing and waning in parallel with exacerbation and resolution of depressive symptoms, respectively.

Corticotropin-releasing factor

Although Saffran and colleagues[10] identified a crude extract that promoted the release of ACTH from the pituitary in 1955, the ultimate regulator of ACTH and cortisol release—corticotrophin-releasing factor (CRF)—was not isolated and chemically characterized until 1981. Working with extracts derived from 500,000 sheep hypothalami, Vale and colleagues[11] at the Salk Institute isolated, synthesized, and elucidated the structure of CRF. This discovery led to the availability of synthetic CRF, which allowed for a comprehensive assessment of the HPA axis. Based on findings from numerous studies, it is clear that CRF coordinates the endocrine, immune, autonomic, and behavioral responses of mammals to stress (**Figure**).[12,13]

In the hypothalamus, CRF is synthesized primarily in the parvocellular neurons of the paraventricular nucleus (PVN). These PVN CRF neurons receive input from a variety of brain regions, including the amygdala, the bed nucleus of the stria terminalis, and the brain stem.[14] Hypothalamic CRFcontaining neurons project to the median eminence.[15]

In response to stress, this neural circuit becomes activated, thereby releasing CRF from median eminence nerve terminals into the hypothalamohypophyseal portal system, where it activates CRF receptors on corticotrophs in the anterior pituitary to promote the synthesis of pro-opiomelanocortin and the release of its major posttranslation products, ACTH and .-endorphin. ACTH, released from the anterior pituitary, stimulates the production and release of cortisol from the adrenal cortex. These same hypothalamic CRF neurons also project to the spinal cord[16] and brainstem nuclei,[17] including the locus caeruleus (LC), the major noradrenergic nucleus in the brain.[18]

Shortly after the isolation and characterization of CRF, a standardized intravenous CRF stimulation test was developed to assess HPA axis activity. In this paradigm, CRF is administered intravenously (usually at a dose of 1 μg/kg or a fixed dose of 100 μg) and the ACTH and cortisol responses are measured at 30-minute intervals over a 2- to 3-hour period.[19] Numerous studies have now documented a blunted ACTH and ß-endorphin response to exogenously administered ovine CRF or human CRF in depressed patients compared with nondepressed persons; the cortisol response in depressed patients and nondepressed control subjects did not consistently differ.[20-24]

It has been hypothesized that the attenuated ACTH response to CRF is due to chronic hypersecretion of CRF from nerve terminals in the median eminence,which results in down-regulation of CRF receptors in the anterior pituitary, and/or to chronic hypercortisolemia and its associated negative feedback. CRF receptor down-regulation results in a reduced responsivity of the anterior pituitary to CRF, as repeatedly demonstrated in laboratory animals.[25-29]

Two CRF receptor subtypes, CRF_1 and CRF_2, with distinct anatomic localization and receptor pharmacology, have been identified in rats and humans.[11,14,15] Both receptors are G-protein coupled receptors (GPCRs) and are positively coupled to adenylyl cyclase via the protein G_s. The CRF_1 receptor is predominantly expressed in the pituitary, cerebellum, and neocortex in the rat.[30] Considerable evidence from laboratory animal studies has shown that CRF_1 receptors may specifically mediate some of the anxiogenic-like behaviors observed after administration of CRF.[31-34]

In agreement with these findings, mice with targeted knockouts of the CRF_1 receptor were found to have an impaired stress response.[35] The CRF1 receptor knockout mice were less anxious than their wild-type litter mates when tested in the elevated plus maze, a paradigm commonly used to assess anxiety-like behavior. In addition, data in these transgenic mice showed a significant reduction in stressinduced release of ACTH and corticosterone.

CRF$_2$ receptor knockout mice have also been generated.[36,37] Deletion of the CRF$_2$ receptor gene during development provided an ambiguous profile, showing increased anxiety in some but not all anxiety tasks[36,37]: in males, but not females[37]; in males and females[36]; or not at all.[38] Thus these studies suggest CRF$_2$ receptor blockade may lead to states of increased anxiety, although it is likely that both the environment and the genetic background on which the knockouts were bred significantly contribute to the behavioral phenotype of these animals.

Research using selective CRF$_2$ receptor agonists and antagonists has been even more inconsistent. Several studies have used the selective CRF$_2$ receptor antagonist antisauvagine-30 (ASV-30),[39] which has been reported to be between 100- and 1000- fold selective for the CRF$_2$ receptor, depending on whether the radiolabeled ligand is sauvagine[39] or ASV-[30,40] respectively. Intraseptal administration of ASV-30 was shown to reduce anxious behavior induced by immobilization stress in the plus maze task or by previous association with foot shock in mice.[41] These behavioral data were corroborated in rats, where intracerebroventricular ASV-30 reduced anxious behavior in the plus maze, defensive withdrawal, and a conditioned anxiety paradigm.[32,42]

Selective agonists at the CRF$_2$ receptor have also been discovered. The peptides urocortin II and urocortin III are structurally and ancestrally related to CRF but show between 100- and 1000-fold selectivity at the CRF$_2$ receptor versus the CRF$_1$ receptor.[43,44] Urocortin III has been shown to mildly suppress locomotion and has an anxiolytic-like profile in mice.[45] However, another study from the same group demonstrated that urocortin II was inactive in the mice in the plus maze after acute administration but increased their exploratory behavior in the plus maze 4 hours later. Thus, compounds reported to be both selective agonists and antagonists at the CRF$_2$ receptor have shown anxiolytic-like effects, making the exact role of this receptor in modulating stress-induced behaviors ambiguous.

Extrahypothalamic CRF circuits and depression

Although initially investigated for its role as one of the key modulators of the HPA axis, further research has revealed that CRF controls not only the neuroendocrine but also the autonomic, immune, and behavioral responses to stress in mammals. Results from both clinical studies and a rich body of literature conducted primarily in rodents and lower primates has highlighted the importance of extrahypothalamic CRF neurons.[12,46,47] In rodents, primates, and humans, CRF and its receptors have been heterogeneously localized in a variety of regions, including the amygdala, thalamus, hippocampus, and prefrontal cortex, among others.[48-51] These brain regions are important in regulating many aspects of the mammalian stress response and affect.

The presence of CRF receptors in both the dorsal raphe and LC, the origin of the major serotonergicand noradrenergic-containing perikarya, respectively, also deserves comment because most available antidepressants, including the tricyclics and SSRIs, are believed to act via modulation of the serotonergic and/or noradrenergic systems. The neuroanatomic proximity of CRF and monoaminergic systems provides evidence for an interaction between CRF systems and antidepressants, thereby suggesting a mechanism by which antidepressants may effect the CRF system.

The involvement of extrahypothalamic CRF systems in the pathophysiology of depression is suggested by numerous studies that have demonstrated elevated CRF concentrations in the cerebrospinal fluid (CSF) of depressed patients,[52-56] although discrepant results have been reported.[57] Elevated CSF CRF concentrations have also been detected in depressed suicide victims.[55] A reduction in concentrations of CRF in CSF has been reported in healthy volunteers treated with the tricyclic antidepressant desipramine[58] and in depressed patients following treatment with fluoxetine[59] or amitriptyline,[60] providing further evidence of an interconnection between antidepressants, monoamine neurons, and CRF systems. Similar effects have been reported after electroconvulsive therapy in depressed patients.[59,61]

Elevated CSF CRF concentrations appear to represent a state, rather than a trait, marker of depression (ie, a marker of current depression rather than a marker of vulnerability to depression).[61] Furthermore, high and/or increasing CSF CRF concentrations despite symptomatic improvement of major depression during antidepressant treatment may be a harbinger of early relapse.[62] Elevated CSF concentrations of CRF are believed to be due to CNS neuronal CRF hypersecretion,[63] which may be acting at sites throughout the brain and contribute to many of the behaviors characteristic of depression.

Consistent with altered concentrations of CRF found in clinical studies of depression, CRF binding site density and messenger RNA (mRNA) expression have shown alterations in both preclinical and clinical studies, presumably in response to changes in CRF availability. Our group has previously reported a marked (23%) reduction in the number of CRF binding sites in the frontal cortex of suicide victims compared with controls[64]; we have now replicated this finding in a second study. Two later studies demonstrated an increase in CRFmRNA expression in

the PVN of depressed patients compared with controls.[65,66]

Increased CRF mRNA and decreased CRF_1 mRNA have also been detected in the brains of suicide victims in subregions of the frontal cortex.[67] Although conducted in different laboratories and on different tissue, and keeping in mind the relative difficulty in obtaining and analyzing human tissue, the general pattern of increased CRF concentrations and/or CRF mRNA and the relative decrease in CRF binding sites is consistent with the well-documented phenomenon of receptor up- and down-regulation.

While the exact mechanism contributing to CRF hyperactivity remains obscure, studies from our group and others have documented long-term persistent increases in HPA axis activity and extrahypothalamic CRF neuronal activity after exposure to early untoward life events, for example, neglect and child abuse, respectively, in both laboratory animals (rats and nonhuman primates) and patients.[68,69] Early life stress apparently permanently sensitizes the HPA axis and extrahypothalamic CRF neurons and leads to a greater risk of depression developing later in life. In several paradigms, early sensitization of CRF systems results in heightened responses to stress later in life.

To measure HPA axis responsivity to stress in humans, the Trier Social Stress Test (TSST) was developed. This laboratory paradigm involves a simulated 10-minute public speech and a difficult mental arithmetic task. The TSST has been validated as a potent activator of the HPA axis in humans.[70] Recently, our group reported increased HPA axis responsivity (ie, elevated plasma ACTH and cortisol concentrations), presumably due to hypersecretion of CRF, after exposure to the TSST in both depressed and nondepressed women who were exposed to severe physical and emotional trauma as children.[71] These data provide evidence that CRF systems are particularly sensitive to the effects of early adverse life events.

Small-molecule CRF antagonists

Although space constraints do not permit an extensive review of the preclinical literature, several additional points are worth noting. Findings from numerous studies have shown that when CRF is directly injected into the CNS of laboratory animals it produces effects reminiscent of the cardinal symptoms of depression, including decreased libido, reduced appetite, weight loss, sleep disturbances, and neophobia.[13] Certainly by the late 1980s, a number of research groups, including our own, had hypothesized that a lipophilic, small-molecule CRF receptor antagonist that readily penetrates the blood-brain barrier after oral administration would represent a novel class of antidepressant and/or anxiolytic agents.

CRF_1 receptor antagonists have elicited activity in animal models of anxiety and depression. CRF receptor antagonists have been tested in many different paradigms, including the elevated plus maze, foot shock, restraint stress, and defensive withdrawal. Pretreatment with CRF receptor antagonists decreases measures of anxiety induced by stressors. There is also some evidence that CRF receptor antagonists may reduce the effects of drug withdrawal and stress-induced relapse to drug seeking in rats.[47,72-74] Based on this premise, newly developed CRF_1 receptor antagonists represent a novel putative class of antidepressants. Such compounds show activity in nearly every preclinical screening test for antidepressants and anxiolytics.

Despite the rich preclinical and clinical literature supporting a potential role for CRF1 receptor antagonists, there has only been 1 published study investigating the effects of a CRF_1 receptor antagonist in humans. A small open-label study examining the effectiveness of R121919, a CRF_1 receptor antagonist, in major depression was completed more than 5 years ago.[75] This study of 20 patients showed that R121919 (5 to 40 mg/d or 40 to 80 mg/d for 30 days) was well tolerated by patients and did not significantly affect plasma ACTH or cortisol concentrations at baseline or following CRF challenge. It is important that the use of any potential CRF antagonist not lead to complete HPA axis blockade and adrenal insufficiency, which can, of course, result in a severe medical emergency. Hamilton Depression Rating Scale and Hamilton Anxiety Scale severity scores were both significantly reduced following 30-day treatment with this drug. Although this small open-label study does not provide unequivocal proof, it does provide further evidence that a selec- tive CRF-receptor antagonist may provide antidepressant and antianxiety properties in humans.[75] Although this drug is no longer in clinical development because of hepatotoxicity, several novel CRF_1 antagonists are currently under investigation.

Conclusions and future directions

Since the discovery of CRF more than 25 years ago, evidence has accumulated indicating a preeminent role for this peptide in the pathophysiology of depression and anxiety. The recent introduction of small-molecule CRF receptor antagonists as a novel class of antidepressant and anxiolytic drugs remains very promising. These compounds block the actions of exogenous and endogenous CRF in a variety of in vivo models, supporting a putative role for these agents in the treatment of stress and/or anxiety and affective disorders. The promising clinical results in patients with depression in the completed open trial of R121919 is of great interest and the results of further studies are eagerly awaited.

As we await the results of additional clinical trials examining the efficacy of CRF_1 receptor antagonists in anxiety and mood disorders, it should be pointed out that these compounds may be beneficial in a broad array of neuropsychiatric disorders (including eating disorders, child abuse, and drug abuse), as well as irritable bowel syndrome and inflammatory diseases. Whether these drugs will be effective as monotherapy or whether they represent an important class of augmenting agents remains to be determined. Furthermore, the development of single photon emission CT and positron emission tomography ligands from these lead compounds for use in neuroimaging studies are likely to be useful in furthering our understanding of the pathophysiology of these mood and anxiety disorders.[76,77]

Drugs mentioned in this article:

Amitriptyline (Limbitrol)
Desipramine (Norpramin, Pertofrane)
Fluoxetine (Prozac, Serafem)

References

1.Gibbons JL,McHugh PR.Plasma cortisol in depressive illness.J Psychiatr Res. 1962;1:162-171.
2. Carpenter WT Jr, Bunney WE Jr. Adrenal cortical activity in depressive illness. Am J Psychiatry. 1971;128:31-40.
3. Sachar EJ, Hellman L, Fukushima DK, Gallagher TF. Cortisol production in depressive illness. A clinical and biochemical clarification. Arch Gen Psychiatry. 1970;23:289-298.
4. Krishnan KR, Doraiswamy PM, Lurie SN, et al. Pituitary size in depression. J Clin Endocrinol Metab. 1991;72:256-259.
5. Amsterdam JD, Marinelli DL, Arger P, Winokur A. Assessment of adrenal gland volume by computed tomography in depressed patients and healthy volunteers: a pilot study. Psychiatry Res. 1987;21:189-197.
6. Nemeroff CB, Krishnan KR, Reed D, et al. Adrenal gland enlargement in major depression.A computed tomographic study. Arch Gen Psychiatry. 1992;49:384-387.
7. Dorovini-Zis K, Zis AP. Increased adrenal weight in victims of violent suicide. Am J Psychiatry. 1987;144:1214-1215.
8. Rubin RT, Phillips JJ, Sadow TF, McCracken JT. Adrenal gland volume in major depression. Increase during the depressive episode and decrease with successful treatment. Arch Gen Psychiatry. 1995;52:213-218.
9. Nemeroff CB, Krishnan KR, Reed D, et al. Adrenal gland enlargement in major depression.A computed tomographic study. Arch Gen Psychiatry. 1992;49:384-387.
10. Saffran M, Schally AV, Benfey BG. Stimulation of the release of corticotropin from the adenohypophysis by a neurohypophysial factor. Endocrinology. 1955;57:439-444.
11. 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.
12. Steckler T, Holsboer F. Corticotropin-releasing hormone receptor subtypes and emotion. Biol Psychiatry. 1999;46:1480-1508.
13.Owens MJ,Nemeroff CB.Physiology and pharmacology of corticotropinreleasing factor. Pharmacol Rev. 1991;43:425-473.
14. Hauger RL, Dautzenberg FM. Regulation of the stress response by corticotropin-releasing factor receptors. In: Conn PM, Freedman ME, eds. Neuroendocrinology in Physiology and Medicine. Totowa, NJ: Humana Press; 2000:261-286.
15. Swanson LW, Sawchenko PE, Rivier J, Vale WW. Organization of ovine corticotrophin-releasing factor immunoreactive cells and fibers in the rat brain: an immunohistochemical study. Neuroendocrinology. 1983;36: 165-186.
16. Kiss JZ, Martos J, Palkovits M. Hypothalamic paraventricular nucleus: a quantitative analysis of cytoarchitectonic subdivisions in the rat. J Comp Neurol. 1991;313:563-573.
17. Swanson LW, Kuypers HG. The paraventricular nucleus of the hypothalamus: cytoarchitectonic subdivisions and organization of projections to the pituitary, dorsal vagal complex, and spinal cord as demonstrated by retrograde fluorescence double-labeling methods. J Comp Neurol. 1980;194:555-570.
18. Reyes BA,Valentino RJ, Xu G,Van Bockstaele EJ. Hypothalamic projections to locus coeruleus neurons in rat brain. Eur J Neurosci. 2005;22: 93-106.
19. Hermus AR, Pieters GF, Smals AG, et al. Plasma adrenocorticotropin, cortisol, and aldosterone responses to corticotrophin-releasing factor: modulatory effect of basal cortisol levels. J Clin Endocrinol Metab. 1984; 58:187-191.
20. Gold PW, Chrousos G, Kellner C, et al. Psychiatric implications of basic and clinical studies with corticotropin-releasing factor. Am J Psychiatry. 1984;141:619-627.
21. Holsboer F, Muller OA, Doerr HG, et al.ACTH and multisteroid responses to corticotropin-releasing factor in depressive illness:relationship to multisteroid responses after ACTH stimulation and dexamethasone suppression. Psychoneuroendocrinology. 1984;9:147-160.
22. Amsterdam JD, Maislin G, Winokur A, et al. The oCRH stimulation test before and after clinical recovery from depression. J Affect Disord. 1988; 14:213-222.

23. Kathol RG, Jaeckle RS, Lopez JF, Meller WH. Consistent reduction of ACTH responses to stimulation with CRH, vasopressin and hypoglycaemia in patients with major depression. Br J Psychiatry. 1989;155:468-478.

24. Young EA, Watson SJ, Kotun J, et al. Beta-lipotropin-beta-endorphin response to low-dose ovine corticotropin releasing factor in endogenous depression. Preliminary studies. Arch Gen Psychiatry. 1990;47:449-457.

25. Wynn PC, Aguilera G, Morell J, Catt KJ. Properties and regulation of high-affinity pituitary receptors for corticotropin-releasing factor.Biochem Biophys Res Commun. 1983;110:602-608.

26. Wynn PC, Hauger RL, Holmes MC, et al. Brain and pituitary receptors for corticotropin releasing factor: localization and differential regulation after adrenalectomy. Peptides. 1984;5:1077-1084.

27. Aguilera G, Wynn PC, Harwood JP, et al. Receptor-mediated actions of corticotropin-releasing factor in pituitary gland and nervous system. Neuroendocrinology. 1986;43:79-88.

28. Holmes MC, Catt KJ, Aguilera G. Involvement of vasopressin in the down-regulation of pituitary corticotropin-releasing factor receptors after adrenalectomy. Endocrinology. 1987;121:2093-2098.

29. Wynn PC, Harwood JP, Catt KJ, Aguilera G. Corticotropin-releasing factor (CRF) induces desensitization of the rat pituitary CRF receptoradenylate cyclase complex. Endocrinology. 1988;122:351-358.

30. Primus RJ, Yevich E, Baltazar C, Gallager DW. Autoradiographic localization of CRF1 and CRF2 binding sites in adult rat brain. Neuropsychopharmacology. 1997;17:308-316.

31. Heinrichs SC, Lapsansky J, Lovenberg TW, et al. Corticotropin-releasing factor CRF1, but not CRF2, receptors mediate anxiogenic-like behavior. Regul Pept. 1997;71:15-21.

32. Takahashi LK. Role of CRF(1) and CRF(2) receptors in fear and anxiety. Neurosci Biobehav Rev. 2001;25:627-636.

33. Bale TL, Picetti R, Contarino A, et al. Mice deficient for both corticotropin- releasing factor receptor 1 (CRFR1) and CRFR2 have an impaired stress response and display sexually dichotomous anxiety-like behavior. J Neurosci. 2002;22:193-199.

34. Risbrough VB, Hauger RL, Roberts AL, et al. Corticotropin-releasing factor receptors CRF1 and CRF2 exert both additive and opposing influences on defensive startle behavior. J Neurosci. 2004;24:6545-6552.

35. Timpl P, Spanagel R, Sillaber I, et al. Impaired stress response and reduced anxiety in mice lacking a functional corticotropin-releasing hormone receptor 1. Nat Genet. 1998;19:162-166.

36. Bale TL, Contarino, A, Smith GW, et al. Mice deficient for corticotropinreleasing hormone receptor-2 display anxiety-like behaviour and are hypersensitive to stress. Nat Genet. 2000;24:410-414.

37. Kishimoto T, Radulovic J, Radulovic M, et al. Deletion of crhr2 reveals an anxiolytic role for corticotropin-releasing hormone receptor-2.Nat Genet. 2000;24:415-419.

38. Coste SC, Kesterson RA, Heldwein KA, et al. Abnormal adaptations to stress and impaired cardiovascular function in mice lacking corticotropinreleasing hormone receptor-2. Nat Genet. 2000;24:403-409.

39. Ruhmann A, Bonk I, Lin CR, et al. Structural requirements for peptidic antagonists of the corticotropin-releasing factor receptor (CRFR): development of CRFR2beta-selective antisauvagine-30. Proc Natl Acad Sci U S A. 1998;95:15264-15269.

40. Higelin J, Py-Lang G, Paternoster C, et al. 125I-Antisauvagine-30: a novel and specific high-affinity radioligand for the characterization of corticotropin-releasing factor type 2 receptors. Neuropharmacology. 2001;40:114-122.

41. Radulovic J, Ruhmann A, Liepold T, Spiess J. Modulation of learning and anxiety by corticotropin-releasing factor (CRF) and stress: differential roles of CRF receptors 1 and 2. J Neurosci. 1999;19:5016-5025.

42. Takahashi LK, Ho SP, Livanov V, et al. Antagonism of CRF(2) receptors produces anxiolytic behavior in animal models of anxiety. Brain Res. 2001;902:135-142.

43. Lewis K, Li C, Perrin MH, et al. Identification of urocortin III, an additional member of the corticotropin-releasing factor (CRF) family with high affinity for the CRF2 receptor. Proc Natl Acad Sci U S A. 2001;98: 7570-7575.

44. Reyes TM, Lewis K, Perrin MH, et al. Urocortin II: a member of the corticotropin-releasing factor (CRF) neuropeptide family that is selectively bound by type 2 CRF receptors. Proc Natl Acad Sci U S A. 2001;98: 2843-2848.

45. Valdez GR, Inoue K, Koob GF, et al. Human urocortin II: mild locomotor suppressive and delayed anxiolytic-like effects of a novel corticotropinreleasing factor related peptide. Brain Res. 2002;943:142-150.

46. Gutman DA, Owens MJ, Nemeroff CB. Corticotropin-releasing factor antagonists as novel psychotherapeutics. Drugs of the Future. 2000;25: 921-931.

47. Gutman DA, Owens MJ, Nemeroff CB. Corticotropin-releasing factor receptor and glucocorticoid receptor antagonists:new approaches to antidepressant treatment. In: den Boer JA, George MS, ter Horst GJ, eds. Current and Future Developments in Psychopharmacology. Amsterdam: Benecke NI; 2005:133-158.

48. Suda T, Tomori N, Tozawa F, et al. Distribution and characterization of immunoreactive corticotropin-releasing factor in human tissues. J Clin Endocrinol Metab. 1984;59:861-866.

49. Charlton BG, Ferrier IN, Perry RH. Distribution of corticotropin-releasing factor-like immunoreactivity in human brain. Neuropeptides. 1987;10: 329-334.

50. Sanchez MM, Young LJ, Plotsky PM, Insel TR. Autoradiographic and in situ hybridization localization of corticotropin-releasing factor 1 and 2 receptors in nonhuman primate brain. J Comp Neurol. 1999;408: 365-377.

51. Van Pett K, Viau V, Bittencourt JC, et al. Distribution of mRNAs encoding CRF receptors in brain and pituitary of rat and mouse. J Comp Neurol. 2000;428:191-212.

52. Banki CM, Bissette G,Arato M, et al. CSF corticotropin-releasing factorlike immunoreactivity in depression and schizophrenia. Am J Psychiatry. 1987;144:873-877.

53. France RD, Urban B, Krishnan KR, et al. CSF corticotropin-releasing factor-like immunoactivity in chronic pain patients with and without major depression. Biol Psychiatry. 1988;23:86-88.
54. Nemeroff CB. The role of corticotropin-releasing factor in the pathogenesis of major depression. Pharmacopsychiatry. 1988;21:76-82.
55. Arato M, Banki CM, Bissette G, Nemeroff CB. Elevated CSF CRF in suicide victims. Biol Psychiatry. 1989;25:355-359.
56. Risch SC, Lewine RJ, Kalin NH, et al. Limbic-hypothalamic-pituitaryadrenal axis activity and ventricular-to-brain ratio studies in affective illness and schizophrenia. Neuropsychopharmacology. 1992;6:95-100.
57. Roy A, Pickar D, Paul S, et al. CSF corticotropin-releasing hormone in depressed patients and normal control subjects. Am J Psychiatry. 1987; 144:641-645.
58. Veith RC, Lewis N, Langohr JI, et al. Effect of desipramine on cerebrospinal fluid concentrations of corticotropin-releasing factor in human subjects. Psychiatry Res. 1993;46:1-8.
59. De Bellis MD, Gold PW, Geracioti TD Jr, et al. Association of fluoxetine treatment with reductions in CSF concentrations of corticotropinreleasing hormone and arginine vasopressin in patients with major depression. Am J Psychiatry. 1993;150:656-657.
60. Heuser I, Bissette G, Dettling M, et al. Cerebrospinal fluid concentrations of corticotropin-releasing hormone, vasopressin, and somatostatin in depressed patients and healthy controls:response to amitriptyline treatment. Depress Anxiety. 1998;8:71-79.
61. Nemeroff CB, Bissette G, Akil H, Fink M. Neuropeptide concentrations in the cerebrospinal fluid of depressed patients treated with electroconvulsive therapy. Corticotrophin-releasing factor, beta-endorphin and somatostatin. Br J Psychiatry. 1991;158:59-63.
62. Banki CM, Karmacsi L, Bissette G, Nemeroff CB. CSF corticotropinreleasing hormone and somatostatin in major depression: response to antidepressant treatment and relapse. Eur Neuropsychopharmacol. 1992; 2:107-113.
63. Post RM, Gold P, Rubinow DR, et al. Peptides in the cerebrospinal fluid of neuropsychiatric patients:an approach to central nervous system peptide function. Life Sci. 1982;31:1-15.
64. Nemeroff CB, Owens MJ, Bissette G, et al. Reduced corticotropin releasing factor binding sites in the frontal cortex of suicide victims. Arch Gen Psychiatry. 1988;45:577-579.
65. Purba JS, Raadsheer FC, Hofman MA, et al. Increased number of corticotropin- releasing hormone expressing neurons in the hypothalamic paraventricular nucleus of patients with multiple sclerosis. Neuroendocrinology. 1995;62:62-70.
66. Raadsheer FC, van Heerikhuize JJ, Lucassen PJ, et al. Corticotropinreleasing hormone mRNA levels in the paraventricular nucleus of patients with Alzheimer's disease and depression. Am J Psychiatry. 1995;152: 1372-1376.
67. Merali Z, Du L, Hrdina P, et al. Dysregulation in the suicide brain: mRNA expression of corticotropin-releasing hormone receptors and GABA(A) receptor subunits in frontal cortical brain region. J Neurosci. 2004;24:1478-1485.
68. Coplan JD, Trost RC, Owens MJ, et al. Cerebrospinal fluid concentrations of somatostatin and biogenic amines in grown primates reared by mothers exposed to manipulated foraging conditions. Arch Gen Psychiatry. 1998;55:473-477.
69. Nemeroff CB. The preeminent role of early untoward experience on vulnerability to major psychiatric disorders: the nature-nurture controversy revisited and soon to be resolved. Mol Psychiatry. 1999;4:106-108.
70. Kirschbaum C, Pirke KM, Hellhammer DH. The 'Trier Social Stress Test'—a tool for investigating psychobiological stress responses in a laboratory setting. Neuropsychobiology. 1993;28:76-81.
71. Heim C, Newport DJ, Bonsall R, et al. Altered pituitary-adrenal axis responses to provocative challenge tests in adult survivors of childhood abuse. Am J Psychiatry. 2001;158:575-581.
72. Erb S, Shaham Y, Stewart J. The role of corticotropin-releasing factor and corticosterone in stress- and cocaine-induced relapse to cocaine seeking in rats. J Neurosci. 1998;18:5529-5536.
73. Shaham Y, Erb S, Leung S, et al. CP-154,526, a selective, non-peptide antagonist of the corticotropin-releasing factor1 receptor attenuates stressinduced relapse to drug seeking in cocaine- and heroin-trained rats. Psychopharmacology (Berl). 1998;137:184-190.
74. Skelton KH, Nemeroff CB, Knight DL, Owens MJ. Chronic administration of the triazolobenzodiazepine alprazolam produces opposite effects on corticotropin-releasing factor and urocortin neuronal systems. J Neurosci. 2000;20:1240-1248.
75. Zobel AW, Nickel T, Kunzel HE, et al. Effects of the high-affinity corticotropin- releasing hormone receptor 1 antagonist R121919 in major depression: the first 20 patients treated. J Psychiatr Res. 2000;34: 171-181.
76. Martarello L, Kilts CD, Ely T, et al. Design, synthesis and evaluation of amino-anilino-pyrimidines as potential SPECT ligands for the CRF1 receptor. International Society of Psychoneuroendocrinology Abstracts. Orlando, USA; 1999:53.
77. Martarello, L, Kilts CD, Ely T, et al. Design, synthesis and characterization of fluorinated- and iodinated-pyrrolo[2,3-d]pyrimidines as candidates for CRF1 receptor PET/SPECT ligands.J Labelled Comp Radiopharm.
42(supp 1):S312-S314.
78. Arborelius L, Owens MJ, Plotsky PM, Nemeroff CB. The role of corticotropin- releasing factor in depression and anxiety disorder. J Endocrinol. 1999;160:1-12.

Evidence-based References

Steckler T, Holsboer F. Corticotropin-releasing hormone receptor subtypes and emotion. Biol Psychiatry. 1999;46:1480-1508.
Strohle A, Holsboer F. Stress responsive neurohormones in depression and anxiety. Pharmacopsychiatry. 2003;36(suppl 3):S207-S214.

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