BioMol Concepts, Vol. 2 (2011), pp. 275–280 • Copyright © by Walter de Gruyter • Berlin • Boston. DOI 10.1515/BMC.2011.022

Review

The role of CRF family peptides in the regulation of food intake and anxiety-like behavior

Naoko Nakayama, Hajime Suzuki, Jiang-Bo Li, Kaori Atsuchi, Minglun Tsai, Haruka Amitani, Akihiro Asakawa* and Akio Inui

Department of Psychosomatic Internal Medicine, Kagoshima University Graduate School of Medical and Dental Sciences, Kagoshima 890-8520, Japan

*Corresponding author
e-mail: asakawa@m2.kufm.kagoshima-u.ac.jp

Abstract

Corticotropin-releasing factor (CRF) and the urocortins (UCN1, UCN2, and UCN3) belong to the CRF family of peptides and are the major regulators of the adaptive response to internal and external stresses. The actions of CRF and UCNs are mediated through two receptor subtypes: CRF receptor 1 (CRFR1) and CRFR2. Their physiological roles, among other functions, include the regulation of food intake and anxiety-like behavior. In this review, we describe the progress that has been made towards understanding how anxiety- and depression-like behavior and food intake are regulated by CRF, UCN1, UCN2, and UCN3.

Keywords: anxiety; corticotropin-releasing factor; food intake; urocortins.

Introduction

Corticotropin-releasing factor (CRF) is a 41-amino acid peptide that was isolated from the ovine hypothalamus and structurally characterized in 1981 (1). CRF is widely expressed in the brain and in peripheral tissues of several species (2–4). In the mammalian brain, CRF is highly expressed in the hypothalamus. Recently, several additional members of the CRF family have been identified: urocortin1 (UCN1) (5), UCN2 (6), and UCN3 (7). CRF and UCNs signal through two receptor subtypes: CRF receptor 1 (CRFR1) and CRFR2 (2) (Figure 1). Rat/human CRF binds with high affinity to CRFR1 and with a lower affinity to CRFR2 (3).

The UCN1 gene was cloned from the rat midbrain in 1995, encoding a 40-amino acid peptide (5). In the mammalian brain, UCN1 mRNA is highly expressed in the Edinger-Westphal nucleus (8). In addition, validated sites of brain UCN1 synthesis include the lateral superior olive, the supraoptic nucleus, the lateral hypothalamic area, and, caudally, several brainstem and spinal cord motoneuron nuclei (8). In the periphery, UCN1 expression has been observed in adipose tissue (9); the heart (10–12); immune system (4, 13), including the spleen and thymus; the testes; the kidneys (14); the adrenal gland (15); and the skin (16, 17). UCN1 is also present in the enteric nervous system of the duodenum, small intestine, and colon (8, 18). UCN1 binds both CRFR1 and CRFR2 with higher affinities than CRF (19).

The mouse UCN2 gene, discovered in 2001, encodes a 38-amino acid peptide (6). Similar to UCN1, UCN2 mRNA is localized in the supraoptic nucleus and magnocellular subdivision of the paraventricular nucleus. Unlike UCN1, UCN2 also has marked expression in the arcuate nucleus of the hypothalamus (6). A survey of peripheral rodent tissue for UCN2 gene expression revealed high levels in the skeletal muscles and skin, moderate levels in the lungs, stomach, adrenal glands, ovaries, brown fat, spleen and thymus, and lower or negligible levels in the testes, kidneys, liver, pancreas, white fat, intestine, heart, and aorta (20, 21). In contrast to UCN1, UCN2 binds CRFR1 with low affinity (6), but unlike CRF, UCN2 binds with high affinity to CRFR2 (5, 6).

The UCN3 gene was also identified in the mouse genome in 2001 (7). Mouse UCN3 mRNA has been found in the brain, including the hypothalamus, amygdala, and brainstem (7). UCN3 gene expression has also been detected in adipose tissue, the heart, skin, thyroid, adrenal glands, β cells of the pancreas, spleen, ovary, placenta, fetal membranes, kidneys, stomach, small intestine, colon, and rectum (22). UCN3 selectively binds CRFR2 (7). In contrast to UCN1, UCN3 binds to CRFR1 only with very low affinity (5, 7).

In recent years, CRF and UCNs have been studied extensively. In this review, we describe the progress that has been made towards understanding how anxiety- and depression-like behavior and food intake are regulated by CRF, UCN1, UCN2, and UCN3.

Effects of CRF family peptides on anxiety-like behavior

CRF

CRF is the key central nervous system mediator of adaptation to stress (23). Intracerebroventricular (ICV) administration of CRF induces anxiety- and depression-like behavior in rats or mice (24–27) and can reproduce some features of irritable bowel syndrome, a stress-related disease, such as diarrhea (28). By contrast, ICV administration of a CRF antagonist has anxiolytic- and antidepressant-like effects (29) and blocks the inhibition of gastric motor function that is

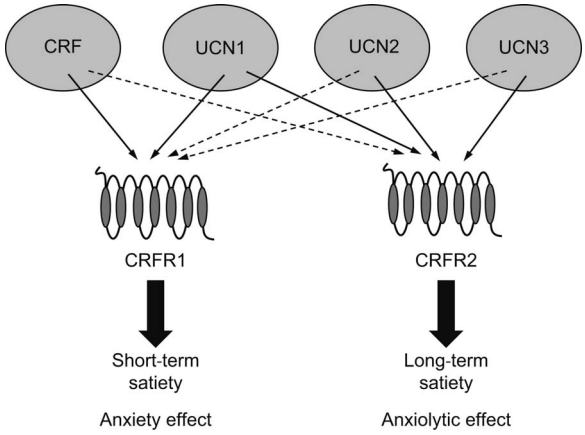

Figure 1 CRF family peptides and CRF receptors.

induced by various stressors (30). Interestingly, pretreatment with gonadotropin-releasing hormone (GnRH) agonists antagonizes CRF-induced anxiety- and depression-like behavior, indicating that GnRH negatively modulates CRF-induced behavioral effects (29). Recently, it was reported that chronic stress increases CRF production in the raphe nucleus associated with decreased serotonin neurotransmission, depression, and anxiety (31). By contrast, steroids increase serotonin effects in the brain by acting through the CRF system, which include decreased CRF transport to serotonin neurons and decreased CRFR1 expression, in conjunction with an increase in UCN1 transported caudally and an increase in CRFR2 and CRF-binding protein expression. As a result, the increase in serotonin action elevates mood, increases stress resistance, and decreases anxiety (32). Nevertheless, CRF-deficient mice display normal behavioral responses to stressors (33). This indicates the existence of developmental rescuing/compensation mechanisms other than the CRF system.

UCN1

Central UCN1 administration induces many neurochemical and behavioral changes. These include behavioral arousal properties in familiar environments and proconvulsant and anxiety-like effects. The anxiety-like properties of central UCN1 administration, mediated at least partly by CRFR1 receptors, have been shown in several conditions, including the open field, the plus maze, light/dark box, defensive withdrawal, and social interaction tests (34–40). The endogenous anxiety-related roles of UCN1 remain uncertain, since Wang et al. reported that UCN1-deficient mice exhibit normal anxiety-like behavior and autonomic responses to stress (41), whereas another UCN1-deficient mouse model showed increased anxiety-like behavior in the plus maze and open field tests (42). The endogenous anxiety-related roles of UCN1 also remain unclear.

UCN2

Unlike CRFR1 agonists, UCN2 does not induce malaise, arousal, or anxiety-like effects at the minimum central doses needed to reduce food intake in rats (6, 24, 43–48) and even opposes the anxiety-like effects of CRF in the open field test (48, 49). However, UCN2 can induce delayed anxiolytic-like effects under high-baseline anxiety conditions in the plus maze (48). Furthermore, ICV administration of high doses of UCN2 to mice increases anxiety-like behavior in the plus maze, as well as acoustic startle responses (50, 51). These results suggest that the effects of exogenous UCN2 on anxiety-like behavior are dependent on the dose of UCN2. UCN2-deficient mice do not exhibit altered anxiety-like behavior in the plus maze, light/dark box, or conditioned fear tests (52). However, UCN1 and UCN2 double-deficient mice show a robust anxiolytic phenotype and modified serotonergic activity in anxiety circuits (53). Moreover, female mice lacking UCN2 exhibit a significant increase in the basal daily rhythms of ACTH and corticosterone and a significant decrease in depression-like behavior (52).

UCN3

UCN3 does not increase anxiety-like behavior in the open field, the plus maze, light/dark box, social interaction, or defensive burying tests, under conditions in which CRFR1 agonists produce anxiety-like changes (49, 54). In fact, ICV administration of UCN3 produces acute anxiolytic-like changes during the plus maze and light/dark box tests (49, 54). Comprehensive behavioral phenotyping of UCN3-deficient mice did not show any alterations in measures of anxiety- or depression-related behaviors (55).

Effects of CRF family peptides on the regulation of food intake

CRF

In both light and dark phases, intraperitoneal (IP) administration of CRF suppresses food intake in mice. Food intake and body weight gain are inhibited by long-term administration (43, 56, 57). The feeding-inhibitory action of IP administered CRF is similar to that of UCN2: more potent than UCN3 but weaker than UCN1 (57). Most previous studies on the action of CRF on feeding behavior have demonstrated that CRF inhibits food intake when administered ICV to fasting rats or mice (6, 58–61). The feeding-inhibitory action of ICV administered CRF is more potent than that of UCN2 or UCN3, but it is weaker than that of UCN1 (61). Effective ICV doses are lower than effective IP doses (57, 61). Wild-type and CRF-deficient mice show similar intake of food pellets and sweetened milk (60).

UCN1

Among the CRF family peptides, UCN1 has the most potent and prolonged inhibitory effect on decreasing food intake and body weight gain, when administered peripherally (56, 57, 62–64). Repeated administration of UCN1 also significantly lowers blood glucose and decreases visceral fat weight in obese mice that are fed on a high-fat diet (57). Centrally

Table 1 Effects of CRF family peptide deficiencies on feeding and anxiety-like behaviors in knockout mice.

	Phenotype of deficient mice			
	$CRF^{-/-}$	$UCN1^{-/-}$	$UCN2^{-/-}$	$UCN3^{-/-}$
Food intake	–	–	–	?
Anxiety-like behavior	–	– ↑	–	–

↑, Stimulation of food intake or anxiety-like behaviors; –, no effects on food intake or anxiety-like behaviors; ?, not reported.

Table 2 Ranking order of potency for feeding inhibition after peripheral or central administration.

IP	UCN1>CRF, UCN2>UCN3
ICV	UCN1>CRF>UCN2, UCN3

IP, Intraperitoneal administration; ICV, intracerebroventricular administration.

administered UCN1 reduces food intake in rats or mice (43, 61, 65). The feeding-inhibitory action of ICV administered UCN1 is the most potent of the CRF family peptides (61). UCN1 infused into the fourth ventricle reduces intraoral sucrose solution intake, even in chronically maintained decerebrate rats, supporting a hindbrain-based mechanism of anorectic action for brainstem UCN1 (66). Nevertheless, UCN1-deficient mice have normal basal feeding behavior (42). This suggests the existence of compensatory mechanisms in deficient mice.

UCN2

In both light and dark phases, IP administration of UCN2 suppresses food intake in mice. Food intake and body weight gain are inhibited by long-term UCN2 administration (57). The feeding-inhibitory action of IP administered UCN2 is more potent than that of UCN3, but it is weaker than that of UCN1 and similar to that of CRF (57). Central administration of UCN2 produces satiation-like changes in meal structure, with food intake reduced at UCN2 doses that do not induce signs of malaise (6, 22, 44–46, 61, 67, 68). The feeding-inhibitory action of ICV administered UCN2 is weaker than that of UCN1 or CRF but similar to that of UCN3 (61). Previous studies have shown that gastric vagal afferent activity is increased by peripheral administration of UCN2 (69). The effect of UCN2 on the afferent activity of the gastric vagal nerve is similar to that of anorexigenic peptides CCK and peptide YY (PYY), and contrary to that of orexigenic peptide ghrelin (70, 71). In addition, CRFR2 binding sites have been characterized on vagal afferent fibers (72). UCN2-deficient mice exhibit normal spontaneous food intake (42, 52). By contrast, UCN2 deficiency blunts the anorectic effects of fenfluramine, suggesting that UCN2 has a downstream role in satiating effects of serotonin (52).

UCN3

Only a few studies have assessed food intake alterations induced by UCN3. In both light and dark phases, IP administration of UCN3 suppresses food intake in mice. Food intake and body weight gain are inhibited by long-term UCN3 administration (57, 64, 73). The feeding-inhibitory action of IP administered UCN3 is the weakest of the CRF family peptides (57). ICV administration of UCN3 decreases food intake in high-fat diet-fed obese mice, as well as in lean mice. The feeding-inhibitory action of ICV administered UCN3 is weaker than that of UCN1 or CRF and similar to that of UCN2 (61).

Perspective

Over the past decade, studies on the CRF family of peptides have revealed their close relation to physiological regulation of anxiety and feeding (Tables 1 and 2). The development of agonists and antagonists of their target receptors will contribute to a better understanding of the role of CRF-like signaling in various pathological states. Recent studies have shown that CRFR1 antagonists including antalarmin and CP-154526 decrease anxiety- and depression-like behaviors (4) and CRFR2 antagonists including antisauvagine-30 attenuate stress-induced anorexia (74, 75). CRF family peptides and CRFRs are therefore promising targets for the treatment of obesity, diabetes, anxiety, and depression.

References

1. Vale W, Spiess J, Rivier C, Rivier J. Characterization of a 41-residue ovine hypothalamic peptide that stimulates secretion of corticotropin and β-endorphin. Science 1981; 213: 1394–7.
2. Chen R, Lewis KA, Perrin MH, Vale WW. Expression cloning of a human corticotropin-releasing-factor receptor. Proc Natl Acad Sci USA 1993; 90: 8967–71.
3. Dieterich KD, Lehnert H, De Souza EB. Corticotropin-releasing factor receptors: an overview. Exp Clin Endocrinol Diabetes 1997; 105: 65–82.
4. Bale TL, Vale WW. CRF and CRF receptors: role in stress responsivity and other behaviors. Annu Rev Pharmacol Toxicol 2004; 44: 525–57.
5. Vaughan J, Donaldson C, Bittencourt J, Perrin MH, Lewis K, Sutton S, Chan R, Turnbull AV, Lovejoy D, Rivier C, Rivier J, Sawchenko PE, Vale W. Urocortin, a mammalian neuropeptide related to fish urotensin I and to corticotropin-releasing factor. Nature 1995; 378: 287–92.
6. Reyes TM, Lewis K, Perrin MH, Kunitake KS, Vaughan J, Arias CA, Hogenesch JB, Gulyas J, Rivier J, Vale WW, Sawchenko PE. 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 USA 2001; 98: 2843–8.
7. Lewis K, Li C, Perrin MH, Blount A, Kunitake K, Donaldson C, Vaughan J, Reyes TM, Gulyas J, Fischer W, Bilezikjian L, Rivier J, Sawchenko PE, Vale WW. 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 USA 2001; 98: 7570–5.
8. Bittencourt JC, Vaughan J, Arias C, Rissman RA, Vale WW, Sawchenko PE. Urocortin expression in rat brain: evidence against a pervasive relationship of urocortin-containing projec-

tions with targets bearing type 2 CRF receptors. J Comp Neurol 1999; 415: 285–312.
9. Seres J, Bornstein SR, Seres P, Willenberg HS, Schulte KM, Scherbaum WA, Ehrhart-Bornstein M. Corticotropin-releasing hormone system in human adipose tissue. J Clin Endocrinol Metab 2004; 89: 965–70.
10. Kimura Y, Takahashi K, Totsune K, Muramatsu Y, Kaneko C, Darnel AD, Suzuki T, Ebina M, Nukiwa T, Sasano H. Expression of urocortin and corticotropin-releasing factor receptor subtypes in the human heart. J Clin Endocrinol Metab 2002; 87: 340–6.
11. Nishikimi T, Miyata A, Horio T, Yoshihara F, Nagaya N, Takishita S, Yutani C, Matsuo H, Matsuoka H, Kangawa K. Urocortin, a member of the corticotropin-releasing factor family, in normal and diseased heart. Am J Physiol Heart Circ Physiol 2000; 279: H3031–9.
12. Okosi A, Brar BK, Chan M, D'Souza L, Smith E, Stephanou A, Latchman DS, Chowdrey HS, Knight RA. Expression and protective effects of urocortin in cardiac myocytes. Neuropeptides 1998; 32: 167–71.
13. Baigent SM. Peripheral corticotropin-releasing hormone and urocortin in the control of the immune response. Peptides 2001; 22: 809–20.
14. Kageyama K, Bradbury MJ, Zhao L, Blount AL, Vale WW. Urocortin messenger ribonucleic acid: tissue distribution in the rat and regulation in thymus by lipopolysaccharide and glucocorticoids. Endocrinology 1999; 140: 5651–8.
15. Fukuda T, Takahashi K, Suzuki T, Saruta M, Watanabe M, Nakata T, Sasano H. Urocortin 1, urocortin 3/stresscopin, and corticotropin-releasing factor receptors in human adrenal and its disorders. J Clin Endocrinol Metab 2005; 90: 4671–8.
16. Slominski A, Wortsman J. Neuroendocrinology of the skin. Endocr Rev 2000; 21: 457–87.
17. Slominski A, Wortsman J, Pisarchik A, Zbytek B, Linton EA, Mazurkiewicz JE, Wei ET. Cutaneous expression of corticotropin-releasing hormone (CRH), urocortin, and CRH receptors. FASEB J 2001; 15: 1678–93.
18. Harada S, Imaki T, Naruse M, Chikada N, Nakajima K, Demura H. Urocortin mRNA is expressed in the enteric nervous system of the rat. Neurosci Lett 1999; 267: 125–8.
19. Donaldson CJ, Sutton SW, Perrin MH, Corrigan AZ, Lewis KA, Rivier JE, Vaughan JM, Vale WW. Cloning and characterization of human urocortin. Endocrinology 1996; 137: 2167–70.
20. Chen A, Blount A, Vaughan J, Brar B, Vale W. Urocortin II gene is highly expressed in mouse skin and skeletal muscle tissues: localization, basal expression in corticotropin-releasing factor receptor (CRFR) 1- and CRFR2-null mice, and regulation by glucocorticoids. Endocrinology 2004; 145: 2445–57.
21. Yamauchi N, Otagiri A, Nemoto T, Sekino A, Oono H, Kato I, Yanaihara C, Shibasaki T. Distribution of urocortin 2 in various tissues of the rat. J Neuroendocrinol 2005; 17: 656–63.
22. Fekete EM, Zorrilla EP. Physiology, pharmacology, and therapeutic relevance of urocortins in mammals: ancient CRF paralogs. Front Neuroendocrinol 2007; 28: 1–27.
23. Arzt E, Holsboer F. CRF signaling: molecular specificity for drug targeting in the CNS. Trends Pharmacol Sci 2006; 27: 531–8.
24. Pelleymounter MA, Joppa M, Ling N, Foster AC. Behavioral and neuroendocrine effects of the selective CRF2 receptor agonists urocortin II and urocortin III. Peptides 2004; 25: 659–66.
25. Britton KT, Morgan J, Rivier J, Vale W, Koob GF. Chlordiazepoxide attenuates response suppression induced by corticotropin-releasing factor in the conflict test. Psychopharmacology (Berl) 1985; 86: 170–4.
26. Britton KT, Lee G, Koob GF. Corticotropin releasing factor and amphetamine exaggerate partial agonist properties of benzodiazepine antagonist Ro 15-1788 in the conflict test. Psychopharmacology (Berl) 1988; 94: 306–11.
27. Swiergiel AH, Zhou Y, Dunn AJ. Effects of chronic footshock, restraint and corticotropin-releasing factor on freezing, ultrasonic vocalization and forced swim behavior in rats. Behav Brain Res 2007; 183: 178–87.
28. Stengel A, Taché Y. Corticotropin-releasing factor signaling and visceral response to stress. Exp Biol Med (Maywood) 2010; 235: 1168–78.
29. Umathe SN, Bhutada PS, Jain NS, Shukla NR, Mundhada YR, Dixit PV. Gonadotropin-releasing hormone agonist blocks anxiogenic-like and depressant-like effect of corticotrophin-releasing hormone in mice. Neuropeptides 2008; 42: 399–410.
30. Taché Y, Martinez V, Million M, Wang L. Stress and the gastrointestinal tract III. Stress-related alterations of gut motor function: role of brain corticotropin-releasing factor receptors. Am J Physiol Gastrointest Liver Physiol 2001; 280: G173–7.
31. Valentino RJ, Lucki I, Van Bockstaele E. Corticotropin-releasing factor in the dorsal raphe nucleus: linking stress coping and addiction. Brain Res 2010; 1314: 29–37.
32. Sanchez RL, Reddy AP, Bethea CL. Ovarian steroid regulation of the midbrain corticotropin releasing factor and urocortin systems in macaques. Neuroscience 2010; 171: 893–909.
33. Dunn AJ, Swiergiel AH. Behavioral responses to stress are intact in CRF-deficient mice. Brain Res 1999; 845: 14–20.
34. Gehlert DR, Shekhar A, Morin SM, Hipskind PA, Zink C, Gackenheimer SL, Shaw J, Fitz SD, Sajdyk TJ. Stress and central urocortin increase anxiety-like behavior in the social interaction test via the CRF1 receptor. Eur J Pharmacol 2005; 509: 145–53.
35. Jones DN, Kortekaas R, Slade PD, Middlemiss DN, Hagan JJ. The behavioural effects of corticotropin-releasing factor-related peptides in rats. Psychopharmacology (Berl) 1998; 138: 124–32.
36. Moreau JL, Kilpatrick G, Jenck F. Urocortin, a novel neuropeptide with anxiogenic-like properties. Neuroreport 1997; 8: 1697–701.
37. Sajdyk TJ, Gehlert DR. Astressin, a corticotropin releasing factor antagonist, reverses the anxiogenic effects of urocortin when administered into the basolateral amygdala. Brain Res 2000; 877: 226–34.
38. Sajdyk TJ, Schober DA, Gehlert DR, Shekhar A. Role of corticotropin-releasing factor and urocortin within the basolateral amygdala of rats in anxiety and panic responses. Behav Brain Res 1999; 100: 207–15.
39. Spina MG, Merlo-Pich E, Akwa Y, Balducci C, Basso AM, Zorrilla EP, Britton KT, Rivier J, Vale WW, Koob GF. Time-dependent induction of anxiogenic-like effects after central infusion of urocortin or corticotropin-releasing factor in the rat. Psychopharmacology (Berl) 2002; 160: 113–21.
40. Zorrilla EP, Schulteis G, Ling N, Koob GF, De Souza EB. Performance-enhancing effects of CRF-BP ligand inhibitors. Neuroreport 2001; 12: 1231–4.
41. Wang X, Su H, Copenhagen LD, Vaishnav S, Pieri F, Shope CD, Brownell WE, De Biasi M, Paylor R, Bradley A. Urocortin-deficient mice display normal stress-induced anxiety behavior and autonomic control but an impaired acoustic startle response. Mol Cell Biol 2002; 22: 6605–10.
42. Vetter DE, Li C, Zhao L, Contarino A, Liberman MC, Smith GW, Marchuk Y, Koob GF, Heinemann SF, Vale W, Lee KF. Urocortin-deficient mice show hearing impairment and increased anxiety-like behavior. Nat Genet 2002; 31: 363–9.

43. Zorrilla EP, Taché Y, Koob GF. Nibbling at CRF receptor control of feeding and gastrocolonic motility. Trends Pharmacol Sci 2003; 24: 421–7.
44. Inoue K, Valdez GR, Reyes TM, Reinhardt LE, Tabarin A, Rivier J, Vale WW, Sawchenko PE, Koob GF, Zorrilla EP. Human urocortin II, a selective agonist for the type 2 corticotropin-releasing factor receptor, decreases feeding and drinking in the rat. J Pharmacol Exp Ther 2003; 305: 385–93.
45. Ohata H, Shibasaki T. Effects of urocortin 2 and 3 on motor activity and food intake in rats. Peptides 2004; 25: 1703–9.
46. Zorrilla EP, Reinhardt LE, Valdez GR, Inoue K, Rivier JE, Vale WW, Koob GF. Human urocortin 2, a corticotropin-releasing factor (CRF) 2 agonist, and ovine CRF, a CRF1 agonist, differentially alter feeding and motor activity. J Pharmacol Exp Ther 2004; 310: 1027–34.
47. de Groote L, Peñalva RG, Flachskamm C, Reul JM, Linthorst AC. Differential monoaminergic, neuroendocrine and behavioural responses after central administration of corticotropin-releasing factor receptor type 1 and type 2 agonists. J Neurochem 2005; 94: 45–56.
48. Valdez GR, Inoue K, Koob GF, Rivier J, Vale W, Zorrilla EP. Human urocortin II: mild locomotor suppressive and delayed anxiolytic-like effects of a novel corticotropin-releasing factor related peptide. Brain Res 2002; 943: 142–50.
49. Venihaki M, Sakihara S, Subramanian S, Dikkes P, Weninger SC, Liapakis G, Graf T, Majzoub JA. Urocortin III, a brain neuropeptide of the corticotropin-releasing hormone family: modulation by stress and attenuation of some anxiety-like behaviours. J Neuroendocrinol 2004; 16: 411–22.
50. Pelleymounter MA, Joppa M, Ling N, Foster AC. Pharmacological evidence supporting a role for central corticotropin-releasing factor 2 receptors in behavioral, but not endocrine, response to environmental stress. J Pharmacol Exp Ther 2002; 302: 145–52.
51. Risbrough VB, Hauger RL, Pelleymounter MA, Geyer MA. Role of corticotropin releasing factor (CRF) receptors 1 and 2 in CRF-potentiated acoustic startle in mice. Psychopharmacology (Berl) 2003; 170: 178–87.
52. Chen A, Zorrilla E, Smith S, Rousso D, Levy C, Vaughan J, Donaldson C, Roberts A, Lee KF, Vale W. Urocortin 2-deficient mice exhibit gender-specific alterations in circadian hypothalamus-pituitary-adrenal axis and depressive-like behavior. J Neurosci 2006; 26: 5500–10.
53. Neufeld-Cohen A, Evans AK, Getselter D, Spyroglou A, Hill A, Gil S, Tsoory M, Beuschlein F, Lowry CA, Vale W, Chen A. Urocortin-1 and -2 double-deficient mice show robust anxiolytic phenotype and modified serotonergic activity in anxiety circuits. Mol Psychiatry 2010; 15: 426–41.
54. Valdez GR, Zorrilla EP, Rivier J, Vale WW, Koob GF. Locomotor suppressive and anxiolytic-like effects of urocortin 3, a highly selective type 2 corticotropin-releasing factor agonist. Brain Res 2003; 980: 206–12.
55. Deussing JM, Breu J, Kühne C, Kallnik M, Bunck M, Glasl L, Yen YC, Schmidt MV, Zurmühlen R, Vogl AM, Gailus-Durner V, Fuchs H, Hölter SM, Wotjak CT, Landgraf R, de Angelis MH, Holsboer F, Wurst W. Urocortin 3 modulates social discrimination abilities via corticotropin-releasing hormone receptor type 2. J Neurosci 2010; 30: 9103–16.
56. Asakawa A, Inui A, Ueno N, Makino S, Fujino MA, Kasuga M. Urocortin reduces food intake and gastric emptying in lean and ob/ob obese mice. Gastroenterology 1999; 116: 1287–92.
57. Tanaka C, Asakawa A, Ushikai M, Sakoguchi T, Amitani H, Terashi M, Cheng K, Chaolu H, Nakamura N, Inui A. Comparison of the anorexigenic activity of CRF family peptides. Biochem Biophys Res Commun 2009; 390: 887–91.
58. Levine AS, Rogers B, Kneip J, Grace M, Morley JE. Effect of centrally administered corticotropin releasing factor (CRF) on multiple feeding paradigms. Neuropharmacology 1983; 22: 337–9.
59. Negri L, Noviello L, Noviello V. Effects of sauvagine, urotensin I and CRF on food intake in rats. Peptides 1985; 6(Suppl 3): 53–7.
60. Swiergiel AH, Dunn AJ. CRF-deficient mice respond like wild-type mice to hypophagic stimuli. Pharmacol Biochem Behav 1999; 64: 59–64.
61. Ushikai M, Asakawa A, Sakoguchi T, Tanaka C, Inui A. Centrally administered urocortin 3 inhibits food intake and gastric emptying in mice. Endocrine 2011; 39: 113–7.
62. Spina M, Merlo-Pich E, Chan RK, Basso AM, Rivier J, Vale W, Koob GF. Appetite-suppressing effects of urocortin, a CRF-related neuropeptide. Science 1996; 273: 1561–4.
63. Wang L, Martínez V, Rivier JE, Taché Y. Peripheral urocortin inhibits gastric emptying and food intake in mice: differential role of CRF receptor 2. Am J Physiol Regul Integr Comp Physiol 2001; 281: R1401–10.
64. Wang L, Stengel A, Goebel M, Martinez V, Gourcerol G, Rivier J, Taché Y. Peripheral activation of corticotropin-releasing factor receptor 2 inhibits food intake and alters meal structures in mice. Peptides 2011; 32: 51–9.
65. Benoit SC, Thiele TE, Heinrichs SC, Rushing PA, Blake KA, Steeley RJ. Comparison of central administration of corticotropin-releasing hormone and urocortin on food intake, conditioned taste aversion, and c-Fos expression. Peptides 2000; 21: 345–51.
66. Daniels D, Markison S, Grill HJ, Kaplan JM. Central structures necessary and sufficient for ingestive and glycemic responses to urocortin I administration. J Neurosci 2004; 24: 11457–62.
67. Fekete EM, Inoue K, Zhao Y, Rivier JE, Vale WW, Szücs A, Koob GF, Zorrilla EP. Delayed satiety-like actions and altered feeding microstructure by a selective type 2 corticotropin-releasing factor agonist in rats: intra-hypothalamic urocortin 3 administration reduces food intake by prolonging the post-meal interval. Neuropsychopharmacology 2007; 32: 1052–68.
68. Cottone P, Sabino V, Nagy TR, Coscina DV, Zorrilla EP. Feeding microstructure in diet-induced obesity susceptible versus resistant rats: central effects of urocortin 2. J Physiol 2007; 583: 487–504.
69. Gourcerol G. Urocortins and cholecystokinin-8 act synergistically to increase satiation in lean but not obese mice: involvement of corticotropin-releasing factor receptor-2 pathway. Endocrinology 2007; 148: 6115–23.
70. Asakawa A, Inui A, Kaga T, Yuzuriha H, Nagata T, Ueno N, Makino S, Fujimiya M, Niijima A, Fujino MA, Kasuga M. Ghrelin is an appetite-stimulatory signal from stomach with structural resemblance to motillin. Gastroenterology 2001; 120: 337–45.
71. Koda S, Date Y, Murakami N, Inomata N, Kazuhiro O, Nakazato M. The role of the vagal nerve in peripheral PYY_{3-36}-induced feeding reduction in rats. Endocrinology 2005; 146: 2369–75.
72. Mercer JG, Lawrence CB, Copeland PA. Corticotropin-releasing factor binding sites undergo axonal transport in the rat vagus nerve. J Neuroendocrinol 1992; 4: 281–5.
73. Terashi M, Asakawa A, Cheng KC, Koyama KI, Chaolu H, Ushikai M, Inui A. Effects of peripherally administered urocortin 3 on feeding behavior and gastric emptying in mice. Exp Ther Med 2011; 2: 333–5.

74. Sekino A, Ohata H, Mano-Otagiri A, Arai K, Shibasaki T. Both corticotropin-releasing factor receptor type 1 and type 2 are involved in stress-induced inhibition of food intake in rats. Psychopharmacology 2004; 176: 30–8.
75. de Gortari P, Mancera K, Cote-Vélez A, Amaya MI, Martínez A, Jaimes-Hoy L, Joseph-Bravo P. Involvement of CRH-R2 receptor in eating behavior and in the response of the HPT axis in rats subjected to dehydration-induced anorexia. Psychoneuroendocrinology 2009; 34: 259–72.

Received March 19, 2011; accepted May 11, 2011