

## Corticotropin-releasing factor receptors (version 2019.4) in the IUPHAR/BPS Guide to Pharmacology Database

Frank M. Dautzenberg<sup>1</sup>, Dimitri E. Grigoriadis<sup>2</sup>, Richard L. Hauger<sup>3</sup>, Victoria B. Risbrough<sup>3</sup>, Thomas Steckler<sup>1</sup>, Wylie W. Vale<sup>4</sup> and Rita J. Valentino<sup>5</sup>

1. Johnson & Johnson Pharmaceutical Research & Development, Belgium
2. Neurocrine Biosciences, USA
3. University of California San Diego, USA
4. Salk Institute, USA
5. Children's Hospital of Philadelphia, USA

### Abstract

Corticotropin-releasing factor (CRF, **nomenclature as agreed by the NC-IUPHAR subcommittee on Corticotropin-releasing Factor Receptors [30]**) receptors are activated by the endogenous peptides [corticotrophin-releasing hormone](#), a 41 amino-acid peptide, [urocortin 1](#), 40 amino-acids, [urocortin 2](#), 38 amino-acids and [urocortin 3](#), 38 amino-acids. CRF<sub>1</sub> and CRF<sub>2</sub> receptors are activated non-selectively by CRH and UCN. CRF<sub>2</sub> receptors are selectively activated by UCN2 and UCN3. Binding to CRF receptors can be conducted using radioligands [<sup>125</sup>I]Tyr<sup>0</sup>-CRF or [<sup>125</sup>I]Tyr<sup>0</sup>-[sauvagine](#) with  $K_d$  values of 0.1-0.4 nM. CRF<sub>1</sub> and CRF<sub>2</sub> receptors are non-selectively antagonized by [α-helical CRF](#), [D-Phe-CRF-\(12-41\)](#) and [astressin](#). CRF<sub>1</sub> receptors are selectively antagonized by small molecules [NBI27914](#), [R121919](#), [antalarmin](#), [CP 154,526](#), [CP 376,395](#). CRF<sub>2</sub> receptors are selectively antagonized by [antisauvagine](#) and [astressin 2B](#).

### Contents

This is a citation summary for Corticotropin-releasing factor receptors in the [Guide to Pharmacology](#) database (GtoPdb). It exists purely as an adjunct to the database to facilitate the recognition of citations to and from the database by citation analyzers. Readers will almost certainly want to visit the relevant sections of the database which are given here under database links.

[GtoPdb](#) is an expert-driven guide to pharmacological targets and the substances that act on them. GtoPdb is a reference work which is most usefully represented as an on-line database. As in any publication this work should be appropriately cited, and the papers it cites should also be recognized. This document provides a

View metadata, citation and similar papers at core.ac.uk

provided by IUPHAR/BPS Guide to Pharmacology CITE

thought to not by COBE those

parts.

Please note that the database version for the citations given in GtoPdb are to the most recent preceding version in which the family or its subfamilies and targets were substantially changed. The links below are to the current version. If you need to consult the cited version, rather than the most recent version, please contact the GtoPdb curators.

## Database links

### Corticotropin-releasing factor receptors

<http://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=19>

### Introduction to Corticotropin-releasing factor receptors

<http://www.guidetopharmacology.org/GRAC/FamilyIntroductionForward?familyId=19>

#### Receptors

##### CRF<sub>1</sub> receptor

<http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=212>

##### CRF<sub>2</sub> receptor

<http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=213>

## References

1. Arai M, Assil IQ and Abou-Samra AB. (2001) Characterization of three corticotropin-releasing factor receptors in catfish: a novel third receptor is predominantly expressed in pituitary and urophysis. *Endocrinology* **142**: 446-54 [PMID:11145609]
2. Arborelius L, Owens MJ, Plotsky PM and Nemeroff CB. (1999) The role of corticotropin-releasing factor in depression and anxiety disorders. *J. Endocrinol.* **160**: 1-12 [PMID:9854171]
3. Bale TL, Contarino A, Smith GW, Chan R, Gold LH, Sawchenko PE, Koob GF, Vale WW and Lee KF. (2000) Mice deficient for corticotropin-releasing hormone receptor-2 display anxiety-like behaviour and are hypersensitive to stress. *Nat. Genet.* **24**: 410-4 [PMID:10742108]
4. Bale TL, Giordano FJ, Hickey RP, Huang Y, Nath AK, Peterson KL, Vale WW and Lee KF. (2002) Corticotropin-releasing factor receptor 2 is a tonic suppressor of vascularization. *Proc. Natl. Acad. Sci. U.S.A.* **99**: 7734-9 [PMID:12032352]
5. Bale TL, Hoshijima M, Gu Y, Dalton N, Anderson KR, Lee KF, Rivier J, Chien KR, Vale WW and Peterson KL. (2004) The cardiovascular physiologic actions of urocortin II: acute effects in murine heart failure. *Proc. Natl. Acad. Sci. U.S.A.* **101**: 3697-702 [PMID:14990799]
6. Bale TL and Vale WW. (2004) CRF and CRF receptors: role in stress responsivity and other behaviors. *Annu. Rev. Pharmacol. Toxicol.* **44**: 525-57 [PMID:14744257]
7. Bittencourt JC, Vaughan J, Arias C, Rissman RA, Vale WW and Sawchenko PE. (1999) Urocortin expression in rat brain: evidence against a pervasive relationship of urocortin-containing projections with targets bearing type 2 CRF receptors. *J. Comp. Neurol.* **415**: 285-312 [PMID:10553117]
8. Cepoi D, Sutton S, Arias C, Sawchenko P and Vale WW. (1999) Ovine genomic urocortin: cloning, pharmacologic characterization, and distribution of central mRNA. *Brain Res. Mol. Brain Res.* **68**: 109-18 [PMID:10320788]
9. Chaki S, Okuyama S, Nakazato A, Kumagai T, Okubo T, Ikeda Y, Oshida Y, Hamajima Y and Tomisawa K. (1999) In vitro pharmacological profile of nonpeptide CRF1 receptor antagonists, CRA1000 and CRA1001. *Eur. J. Pharmacol.* **371**: 205-11 [PMID:10357258]
10. Chalmers DT, Lovenberg TW and De Souza EB. (1995) 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.* **15**: 6340-50 [PMID:7472399]
11. Chalmers DT, Lovenberg TW, Grigoriadis DE, Behan DP and De Souza EB. (1996) Corticotrophin-releasing factor receptors: from molecular biology to drug design. *Trends Pharmacol. Sci.* **17**: 166-72 [PMID:8984745]
12. Chang CP, Pearce 2nd RV, O'Connell S and Rosenfeld MG. (1993) Identification of a seven transmembrane helix receptor for corticotropin-releasing factor and sauvagine in mammalian brain. *Neuron* **11**: 1187-95 [PMID:8274282]
13. Chen C, Dagnino R, De Souza EB, Grigoriadis DE, Huang CQ, Kim KI, Liu Z, Moran T, Webb TR and Whitten JP *et al.*. (1996) Design and synthesis of a series of non-peptide high-affinity human corticotropin-releasing factor1 receptor antagonists. *J. Med. Chem.* **39**: 4358-60 [PMID:8893829]

14. Chen R, Lewis KA, Perrin MH and Vale WW. (1993) Expression cloning of a human corticotropin-releasing-factor receptor. *Proc. Natl. Acad. Sci. U.S.A.* **90**: 8967-71 [PMID:7692441]
15. Chen YL, Obach RS, Braselton J, Corman ML, Forman J, Freeman J, Gallaschun RJ, Mansbach R, Schmidt AW and Sprouse JS *et al.*. (2008) 2-aryloxy-4-alkylaminopyridines: discovery of novel corticotropin-releasing factor 1 antagonists. *J. Med. Chem.* **51**: 1385-92 [PMID:18288792]
16. Coste SC, Kesterson RA, Heldwein KA, Stevens SL, Heard AD, Hollis JH, Murray SE, Hill JK, Pantely GA and Hohimer AR *et al.*. (2000) Abnormal adaptations to stress and impaired cardiovascular function in mice lacking corticotropin-releasing hormone receptor-2. *Nat. Genet.* **24**: 403-9 [PMID:10742107]
17. Dautzenberg FM, Dietrich K, Palchadhuri MR and Spiess J. (1997) Identification of two corticotropin-releasing factor receptors from *Xenopus laevis* with high ligand selectivity: unusual pharmacology of the type 1 receptor. *J. Neurochem.* **69**: 1640-9 [PMID:9326293]
18. Dautzenberg FM, Gutknecht E, Van der Linden I, Olivares-Reyes JA, Dürrenberger F and Hauger RL. (2004) Cell type specific calcium signaling by corticotropin-releasing factor type 1 (CRF1) and 2a (CRF2(a)) receptors: Gq coupling in human embryonic kidney 293 but not SK-N-MC neuroblastoma cells. *Biochem Pharmacol.* **68**: 1833-1844 [PMID:15450949]
19. Dautzenberg FM and Hauger RL. (2002) The CRF peptide family and their receptors: yet more partners discovered. *Trends Pharmacol Sci.* **23**: 71-77 [PMID:11830263]
20. Dautzenberg FM, Huber G, Higelin J, Py-Lang G and Kilpatrick GJ. (2000) Evidence for the abundant expression of arginine 185 containing human CRF(2alpha) receptors and the role of position 185 for receptor-ligand selectivity. *Neuropharmacology* **39**: 1368-76 [PMID:10818253]
21. Dautzenberg FM, Kilpatrick GJ, Hauger RL and Moreau J. (2001) Molecular biology of the CRH receptors - in the mood. *Peptides* **22**: 753-60 [PMID:11337088]
22. Dautzenberg FM, Py-Lang G, Higelin J, Fischer C, Wright MB and Huber G. (2001) Different binding modes of amphibian and human corticotropin-releasing factor type 1 and type 2 receptors: evidence for evolutionary differences. *J. Pharmacol. Exp. Ther.* **296**: 113-20 [PMID:11123370]
23. Dautzenberg FM and Wille S. (2004) Binding differences of human and amphibian corticotropin-releasing factor type 1 (CRF(1)) receptors: identification of amino acids mediating high-affinity astressin binding and functional antagonism. *Regul. Pept.* **118**: 165-73 [PMID:15003833]
24. de Groef B, Grommen SV, Mertens I, Schoofs L, Kühn ER and Darras VM. (2004) Cloning and tissue distribution of the chicken type 2 corticotropin-releasing hormone receptor. *Gen. Comp. Endocrinol.* **138**: 89-95 [PMID:15242755]
25. De Souza EB, Perrin MH, Insel TR, Rivier J, Vale WW and Kuhar MJ. (1984) Corticotropin-releasing factor receptors in rat forebrain: autoradiographic identification. *Science.* **224**: 1449-1451 [PMID:6328656]
26. Donaldson CJ, Sutton SW, Perrin MH, Corrigan AZ, Lewis KA, Rivier JE, Vaughan JM and Vale WW. (1996) Cloning and characterization of human urocortin. *Endocrinology* **137**: 2167-70 [PMID:8612563]
27. Dunn AJ and Berridge CW. (1990) Physiological and behavioral responses to corticotropin-releasing factor administration: is CRF a mediator of anxiety or stress responses? *Brain Res. Brain Res. Rev.* **15**: 71-100 [PMID:1980834]
28. Gully D, Geslin M, Serva L, Fontaine E, Roger P, Lair C, Darre V, Marcy C, Rouby PE and Simiand J *et al.*. (2002) 4-(2-Chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-(2-propynyl)-1,3-thiazol-2-amine hydrochloride (SSR125543A): a potent and selective corticotrophin-releasing factor(1) receptor antagonist. I. Biochemical and pharmacological characterization. *J. Pharmacol. Exp. Ther.* **301**: 322-32 [PMID:11907190]
29. Hauger RL and Dautzenberg FM. (1999) Regulation of the stress response by corticotropin-releasing factor receptors. In *Physiology and Medicine* Edited by Conn PM, Freedman ME: Humana Press Inc.: 261-286 [ISBN: 0896037250]
30. Hauger RL, Grigoriadis DE, Dallman MF, Plotsky PM, Vale WW and Dautzenberg FM. (2003) International Union of Pharmacology. XXXVI. Current status of the nomenclature for receptors for corticotropin-releasing factor and their ligands. *Pharmacol. Rev.* **55**: 21-6 [PMID:12615952]
31. He L, Gilligan PJ, Zaczek R, Fitzgerald LW, McElroy J, Shen HS, Saye JA, Kalin NH, Shelton S and Christ

- D *et al.*. (2000) 4-(1,3-Dimethoxyprop-2-ylamino)-2,7-dimethyl-8-(2, 4-dichlorophenyl)pyrazolo[1,5-a]-1,3,5-triazine: a potent, orally bioavailable CRF(1) receptor antagonist. *J. Med. Chem.* **43**: 449-56 [PMID:10669572]
32. Heinrichs SC and De Souza EB. (1999) Corticotropin-releasing factor antagonists, binding-protein and receptors: implications for central nervous system disorders. *Baillieres Best Pract Res Clin Endocrinol Metab* **13**: 541-54 [PMID:10903813]
33. Heinrichs SC and Koob GF. (2004) Corticotropin-releasing factor in brain: a role in activation, arousal, and affect regulation. *J. Pharmacol. Exp. Ther.* **311**: 427-40 [PMID:15297468]
34. Heinrichs SC, Lapsansky J, Lovenberg TW, De Souza EB and Chalmers DT. (1997) Corticotropin-releasing factor CRF1, but not CRF2, receptors mediate anxiogenic-like behavior. *Regul. Pept.* **71**: 15-21 [PMID:9299637]
35. Ho SP, Takahashi LK, Livanov V, Spencer K, Leshner T, Maciag C, Smith MA, Rohrbach KW, Hartig PR and Arneric SP. (2001) Attenuation of fear conditioning by antisense inhibition of brain corticotropin releasing factor-2 receptor. *Brain Res. Mol. Brain Res.* **89**: 29-40 [PMID:11311973]
36. Hollenstein K, Kean J, Bortolato A, Cheng RK, Doré AS, Jazayeri A, Cooke RM, Weir M and Marshall FH. (2013) Structure of class B GPCR corticotropin-releasing factor receptor 1. *Nature* **499**: 438-43 [PMID:23863939]
37. Hsu SY and Hsueh AJ. (2001) Human stresscopin and stresscopin-related peptide are selective ligands for the type 2 corticotropin-releasing hormone receptor. *Nat. Med.* **7**: 605-11 [PMID:11329063]
38. Kageyama K, Bradbury MJ, Zhao L, Blount AL and Vale WW. (1999) Urocortin messenger ribonucleic acid: tissue distribution in the rat and regulation in thymus by lipopolysaccharide and glucocorticoids. *Endocrinology* **140**: 5651-8 [PMID:10579329]
39. Kishimoto T, Pearse 2nd RV, Lin CR and Rosenfeld MG. (1995) A sauvagine/corticotropin-releasing factor receptor expressed in heart and skeletal muscle. *Proc. Natl. Acad. Sci. U.S.A.* **92**: 1108-12 [PMID:7755719]
40. Kostich WA, Chen A, Sperle K and Largent BL. (1998) Molecular identification and analysis of a novel human corticotropin-releasing factor (CRF) receptor: the CRF2gamma receptor. *Mol. Endocrinol.* **12**: 1077-85 [PMID:9717834]
41. Lawrence AJ, Krstew EV, Dautzenberg FM and Rühmann A. (2002) The highly selective CRF(2) receptor antagonist K41498 binds to presynaptic CRF(2) receptors in rat brain. *Br. J. Pharmacol.* **136**: 896-904 [PMID:12110614]
42. Lederis K, Letter A, McMaster D, Moore G and Schlesinger D. (1982) Complete amino acid sequence of urotensin I, a hypotensive and corticotropin-releasing neuropeptide from *Catostomus*. *Science* **218**: 162-5 [PMID:6981844]
43. Lewis K, Li C, Perrin MH, Blount A, Kunitake K, Donaldson C, Vaughan J, Reyes TM, Gulyas J and Fischer W *et al.*. (2001) 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.* **98**: 7570-5 [PMID:11416224]
44. Li C, Chen P, Vaughan J, Blount A, Chen A, Jamieson PM, Rivier J, Smith MS and Vale W. (2003) Urocortin III is expressed in pancreatic beta-cells and stimulates insulin and glucagon secretion. *Endocrinology* **144**: 3216-24 [PMID:12810578]
45. Li C, Vaughan J, Sawchenko PE and Vale WW. (2002) Urocortin III-immunoreactive projections in rat brain: partial overlap with sites of type 2 corticotrophin-releasing factor receptor expression. *J. Neurosci.* **22**: 991-1001 [PMID:11826127]
46. Liaw CW, Lovenberg TW, Barry G, Oltersdorf T, Grigoriadis DE and de Souza EB. (1996) Cloning and characterization of the human corticotropin-releasing factor-2 receptor complementary deoxyribonucleic acid. *Endocrinology* **137**: 72-7 [PMID:8536644]
47. Liebsch G, Landgraf R, Engelmann M, Lörscher P and Holsboer F. (1999) Differential behavioural effects of chronic infusion of CRH 1 and CRH 2 receptor antisense oligonucleotides into the rat brain. *J Psychiatr Res* **33**: 153-63 [PMID:10221747]

48. Lovenberg TW, Chalmers DT, Liu C and De Souza EB. (1995) CRF2 alpha and CRF2 beta receptor mRNAs are differentially distributed between the rat central nervous system and peripheral tissues. *Endocrinology*. **136**: 4139-4142 [PMID:7544278]
49. Lovenberg TW, Liaw CW, Grigoriadis DE, Clevenger W, Chalmers DT, De Souza EB and Oltersdorf T. (1995) Cloning and characterization of a functionally distinct corticotropin-releasing factor receptor subtype from rat brain. *Proc. Natl. Acad. Sci. U.S.A.* **92**: 836-40 [PMID:7846062]
50. Lundkvist J, Chai Z, Teheranian R, Hasanvan H, Bartfai T, Jenck F, Widmer U and Moreau JL. (1996) A non peptidic corticotropin releasing factor receptor antagonist attenuates fever and exhibits anxiolytic-like activity. *Eur. J. Pharmacol.* **309**: 195-200 [PMID:8874139]
51. Montecucchi PC and Henschen A. (1981) Amino acid composition and sequence analysis of sauvagine, a new active peptide from the skin of *Phyllomedusa sauvagei*. *Int. J. Pept. Protein Res.* **18**: 113-20 [PMID:7309372]
52. Myers DA, Trinh JV and Myers TR. (1998) Structure and function of the ovine type 1 corticotropin releasing factor receptor (CRF1) and a carboxyl-terminal variant. *Mol. Cell. Endocrinol.* **144**: 21-35 [PMID:9863624]
53. Nappi RE and Rivest S. (1995) Stress-induced genetic expression of a selective corticotropin-releasing factor-receptor subtype within the rat ovaries: an effect dependent on the ovulatory cycle. *Biol. Reprod.* **53**: 1417-28 [PMID:8562699]
54. Okawara Y, Morley SD, Burzio LO, Zwiers H, Lederis K and Richter D. (1988) Cloning and sequence analysis of cDNA for corticotropin-releasing factor precursor from the teleost fish *Catostomus commersoni*. *Proc. Natl. Acad. Sci. U.S.A.* **85**: 8439-43 [PMID:3186733]
55. Oshida Y, Ikeda Y, Chaki S and Okuyama S. (2004) Monkey corticotropin-releasing factor1 receptor: Complementary DNA cloning and pharmacological characterization. *Life Sci.* **74**: 1911-1924 [PMID:14761672]
56. Pal K, Swaminathan K, Xu HE and Pioszak AA. (2010) Structural basis for hormone recognition by the Human CRFR2{alpha} G protein-coupled receptor. *J. Biol. Chem.* **285**: 40351-61 [PMID:20966082]
57. Palchaudhuri MR, Hauger RL, Wille S, Fuchs E and Dautzenberg FM. (1999) Isolation and pharmacological characterization of two functional splice variants of corticotropin-releasing factor type 2 receptor from *Tupaia belangeri*. *J. Neuroendocrinol.* **11**: 419-28 [PMID:10336722]
58. Palchaudhuri MR, Wille S, Mevenkamp G, Spiess J, Fuchs E and Dautzenberg FM. (1998) Corticotropin-releasing factor receptor type 1 from *Tupaia belangeri*--cloning, functional expression and tissue distribution. *Eur. J. Biochem.* **258**: 78-84 [PMID:9851694]
59. Perkins AV, Wolfe CD, Eben F, Soothill P and Linton EA. (1995) Corticotrophin-releasing hormone-binding protein in human fetal plasma. *J. Endocrinol.* **146**: 395-401 [PMID:7595134]
60. Perrin MH, Donaldson CJ, Chen R, Lewis KA and Vale WW. (1993) Cloning and functional expression of a rat brain corticotropin releasing factor (CRF) receptor. *Endocrinology* **133**: 3058-61 [PMID:8243338]
61. Perrin MH, Sutton SW, Cervini LA, Rivier JE and Vale WW. (1999) Comparison of an agonist, urocortin, and an antagonist, astressin, as radioligands for characterization of corticotropin-releasing factor receptors. *J. Pharmacol. Exp. Ther.* **288**: 729-34 [PMID:9918582]
62. Pioszak AA, Parker NR, Suino-Powell K and Xu HE. (2008) Molecular recognition of corticotropin-releasing factor by its G-protein-coupled receptor CRFR1. *J. Biol. Chem.* **283**: 32900-12 [PMID:18801728]
63. Pohl S, Darlison MG, Clarke WC, Lederis K and Richter D. (2001) Cloning and functional pharmacology of two corticotropin-releasing factor receptors from a teleost fish. *Eur. J. Pharmacol.* **430**: 193-202 [PMID:11711031]
64. Potter E, Sutton S, Donaldson C, Chen R, Perrin M, Lewis K, Sawchenko PE and Vale W. (1994) Distribution of corticotropin-releasing factor receptor mRNA expression in the rat brain and pituitary. *Proc. Natl. Acad. Sci. U.S.A.* **91**: 8777-81 [PMID:8090722]
65. Reyes TM, Lewis K, Perrin MH, Kunitake KS, Vaughan J, Arias CA, Hogenesch JB, Gulyas J, Rivier J and Vale WW *et al.*. (2001) 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.* **98**: 2843-8 [PMID:11226328]



66. Rühmann A, Chapman J, Higelin J, Butscha B and Dautzenberg FM. (2002) Design, synthesis and pharmacological characterization of new highly selective CRF(2) antagonists: development of 123I-K31440 as a potential SPECT ligand. *Peptides* **23**: 453-60 [PMID:11835994]
67. Smagin GN, Heinrichs SC and Dunn AJ. (2001) The role of CRH in behavioral responses to stress. *Peptides* **22**: 713-24 [PMID:11337084]
68. Smith GW, Aubry JM, Dellu F, Contarino A, Bilezikjian LM, Gold LH, Chen R, Marchuk Y, Hauser C and Bentley CA *et al.*. (1998) Corticotropin releasing factor receptor 1-deficient mice display decreased anxiety, impaired stress response, and aberrant neuroendocrine development. *Neuron* **20**: 1093-102 [PMID:9655498]
69. Stenzel P, Kesterson R, Yeung W, Cone RD, Rittenberg MB and Stenzel-Poore MP. (1995) Identification of a novel murine receptor for corticotropin-releasing hormone expressed in the heart. *Mol. Endocrinol.* **9**: 637-45 [PMID:7565810]
70. Stenzel-Poore MP, Heldwein KA, Stenzel P, Lee S and Vale WW. (1992) Characterization of the genomic corticotropin-releasing factor (CRF) gene from *Xenopus laevis*: two members of the CRF family exist in amphibians. *Mol. Endocrinol.* **6**: 1716-24 [PMID:1448118]
71. Swanson LW, Sawchenko PE, Rivier J and Vale WW. (1983) Organization of ovine corticotropin-releasing factor immunoreactive cells and fibers in the rat brain: an immunohistochemical study. *Neuroendocrinology* **36**: 165-86 [PMID:6601247]
72. Sánchez MM, Young LJ, Plotsky PM and Insel TR. (1999) Autoradiographic and in situ hybridization localization of corticotropin-releasing factor 1 and 2 receptors in nonhuman primate brain. *J. Comp. Neurol.* **408**: 365-77 [PMID:10340512]
73. Tache Y, Martinez V, Wang L and Million M. (2004) CRF1 receptor signaling pathways are involved in stress-related alterations of colonic function and viscerosensitivity: implications for irritable bowel syndrome. *Br J Pharmacol.* **141**: 1321-1330 [PMID:15100165]
74. Takahashi LK. (2001) Role of CRF(1) and CRF(2) receptors in fear and anxiety. *Neurosci Biobehav Rev.* **25**: 627-636 [PMID:11801288]
75. Timpl P, Spanagel R, Sillaber I, Kresse A, Reul JM, Stalla GK, Blanquet V, Steckler T, Holsboer F and Wurst W. (1998) Impaired stress response and reduced anxiety in mice lacking a functional corticotropin-releasing hormone receptor 1. *Nat Genet.* **19**: 162-166 [PMID:9620773]
76. Valdenaire O, Giller T, Breu V, Gottowik J and Kilpatrick G. (1997) A new functional isoform of the human CRF2 receptor for corticotropin-releasing factor. *Biochim. Biophys. Acta* **1352**: 129-32 [PMID:9199241]
77. Vale W, Spiess J, Rivier C and Rivier J. (1981) Characterization of a 41-residue ovine hypothalamic peptide that stimulates secretion of corticotropin and beta-endorphin. *Science* **213**: 1394-7 [PMID:6267699]
78. Vale W, Vaughan J and Perrin M. (1997) Corticotropin-releasing factor (CRF) family of ligands and their receptors. *The Endocrinologist* **7**: S3-S9
79. Vaughan J, Donaldson C, Bittencourt J, Perrin MH, Lewis K, Sutton S, Chan R, Turnbull AV, Lovejoy D and Rivier C *et al.*. (1995) Urocortin, a mammalian neuropeptide related to fish urotensin I and to corticotropin-releasing factor. *Nature* **378**: 287-92 [PMID:7477349]
80. Vita N, Laurent P, Lefort S, Chalon P, Lelias JM, Kaghad M, Le Fur G, Caput D and Ferrara P. (1993) Primary structure and functional expression of mouse pituitary and human brain corticotrophin releasing factor receptors. *FEBS Lett.* **335**: 1-5 [PMID:8243652]
81. Webster EL, Lewis DB, Torpy DJ, Zachman EK, Rice KC and Chrousos GP. (1996) In vivo and in vitro characterization of antalarmin, a nonpeptide corticotropin-releasing hormone (CRH) receptor antagonist: suppression of pituitary ACTH release and peripheral inflammation. *Endocrinology* **137**: 5747-50 [PMID:8940412]
82. Wynn PC, Hauger RL, Holmes MC, Millan MA, Catt KJ and Aguilera G. (1984) Brain and pituitary receptors for corticotropin releasing factor: localization and differential regulation after adrenalectomy. *Peptides.* **5**: 1077-1084 [PMID:6099558]
83. Yu J, Xie LY and Abou-Samra AB. (1996) Molecular cloning of a type A chicken corticotropin-releasing factor receptor with high affinity for urotensin I. *Endocrinology* **137**: 192-7 [PMID:8536612]

84. Zhao L, Donaldson CJ, Smith GW and Vale WW. (1998) The structures of the mouse and human urocortin genes (Ucn and UCN). *Genomics* **50**: 23-33 [[PMID:9628819](#)]
85. Zobel AW, Nickel T, Künzel HE, Ackl N, Sonntag A, Ising M and Holsboer F. (2000) Effects of the high-affinity corticotropin-releasing hormone receptor 1 antagonist R121919 in major depression: the first 20 patients treated. *J Psychiatr Res* **34**: 171-81 [[PMID:10867111](#)]