

Corticotropin-Releasing Factor Receptors

Key References

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Overview

Corticotropin-releasing factor (CRF) has been widely implicated as playing a major role in modulating the endocrine, autonomic, behavioral and immune responses to stress. The cloning of multiple receptors for CRF, identification of additional endogenous ligands, as well as the discovery of non-peptide receptor antagonists for CRF receptors have begun a new era of CRF study.

Presently, there are five distinct targets for CRF with unique cDNA sequences, pharmacology and localization. These fall into three distinct classes, encoded by three different genes and have been termed the CRF₁, CRF₂ receptors (belonging to the superfamily of G protein-coupled receptors) and the CRF-binding protein. The CRF₂ receptor exists as three splice variants of the same gene that have now been designated CRF_{2(a)}, CRF_{2(b)} and CRF_{2(c)} as per IUPHAR nomenclature. The pharmacology and localization of these proteins in brain and periphery has been well established. In brain, the CRF₁ receptor is localized primarily to cortical and cerebellar regions while the CRF_{2(a)} receptor is localized to subcortical regions including the lateral septum, and paraventricular and ventromedial nuclei of the hypothalamus. Peripherally, the CRF₁ receptor is localized in the gut and uterus while the CRF_{2(b)} receptor is primarily localized to heart, skeletal muscle and to cerebral arterioles and choroid plexus. The CRF_{2(c)} receptor has thus far been identified only in human amygdala.

The natural mammalian ligands oCRF and r/hCRF have high affinity for the CRF₁ receptor subtype, with lower affinity for the CRF₂ receptor family making them good labels for the CRF₁ receptor. On the other hand, the non-mammalian ligand

[¹²⁵I]-sauvagine and synthetic [¹²⁵I]-antisauvagine-30 have been characterized as high affinity ligands for the CRF₂ receptor. These radioligands have become useful tools in the discovery of non-peptide, high affinity, and selective receptor antagonists. Recently, the discovery of urocortin 2, and urocortin 3, endogenous mammalian peptides that have high affinity for the CRF₂ receptor and very low affinity for the CRF₁ receptor, has offered new insights into the role and function of this receptor subtype.

Non-peptide CRF₁ receptor antagonists that can specifically and selectively block the CRF₁ receptor subtype have been a major focus of discovery research over the past decade. Compounds such as CP 154,526, NBI 27914, antalarmin, DMP 696, NBI 30775/R121919 and many others have all demonstrated *in vitro* inhibition of CRF-induced second messenger or other functional effects. In addition, when administered peripherally, these compounds compete for *ex vivo* [¹²⁵I]-sauvagine binding to CRF₁ receptors in brain sections demonstrating their ability to cross the blood brain barrier. In *in vivo* studies, peripheral administration of these compounds attenuates CRF or stress-induced behavioral changes, elevations in plasma ACTH levels, seizure activity or colonic motility. Furthermore, in a preliminary clinical phase IIA study, the CRF₁ receptor antagonist NBI 30775/R121919 was found to have activity in patients with Major Depressive Disorder.

Although the primary focus for CRF₁ receptor selective antagonists is still in the area of anxiety and depression, different animal models have demonstrated a beneficial effect of these molecules in the neurodegeneration associated with stroke, the pain associated with various inflamma-

tory responses and a potential utility in GI disorders such as irritable bowel syndrome. Although selective high-affinity non-peptide small molecules have not yet been identified for the CRF₂ receptor subtype, the potential indications for such molecules range from eating disorders to cerebrovascular disease, migraine and congestive heart failure. It is also tempting to speculate that as more information becomes available through the drug discovery efforts of both the pharmaceutical industry and academic research, the interaction between the various receptor subtypes may play a further unique role in the etiology of various disease states.

Corticotropin-Releasing Factor Receptors

CURRENTLY ACCEPTED NAME ^a	CRF1 (human, rat, mouse)	CRF _{2(a)}	CRF _{2(b)}	CRF _{2(c)}	CRF-BP (human, rat)
ALTERNATE NAME(S)	CRF-RA (human, rat), PC-CRF (rat, mouse)	CRF _{2α} (human, rat)	CRF _{2β} (human, rat, mouse), CRF-RB (mouse), HM-CRF (mouse)	CRF _{2γ} (human)	—
STRUCTURAL INFORMATION	415 aa (rat), 415 aa (human), 415 aa (mouse)	411 aa (rat), 411 aa (human)	431 aa (rat), 431 aa (mouse), 431 aa (human)	397 aa (human)	322 aa (rat), 322 aa (human)
AGONISTS ^b	CRF (C3042), UCN1 (U4127 (h), U6631 (r))	CRF (C3042), UCN1 (U4127 (h), U6631 (r)), UCN2 (U9507 (m)), UCN3 (U1008 (h), U0883 (m))	CRF (C3042), UCN1 (U4127 (h), U6631 (r)), UCN2 (U9507 (m)), UCN3 (U1008 (h), U0883 (m))	CRF (C3042), UCN1 (U4127 (h), U6631 (r)) UCN2 (U9507 (m))	CRF (C3042) UCN1 (U4127 (h), U6631 (r))
PEPTIDE RANK ORDER OF POTENCIES	Sauvagine (S3884) = Urotensin I (U7253) = UCN1 (U4127 (h), U6631 (r)) = oCRF (C3167) = r/hCRF (C3042) = bCRF (C2671) > Astressin (A4933) > D-Phe r/hCRF(12-41) > α-helical oCRF(9-41) (C2917) >> UCN2 (U9507 (m)), Astressin _{2B} (A5227) r/hCRF(6-33) (C0961), r/hCRF(9-33), r/hCRF(1-41)OH, VIP (V6130), AVP (V9879 , V0377)	Sauvagine (S3884) = Urotensin I (U7253) = UCN1 (U4127 (h), U6631 (r)) = UCN2 (U9507 (m)) = UCN3 (U1008) = Astressin _{2B} (A5227) > r/hCRF (C3042) > oCRF (C3167) > bCRF (C2671) > D-Phe r/hCRF(12-41) > α-helical oCRF(9-41) (C2917) >> r/hCRF(6-33) (C0961), r/hCRF(9-33), r/hCRF(1-41)OH, VIP (V6130), AVP (V9879 , V0377)	r/hCRF (C3042) = Sauvagine (S3884) = Urotensin I (U7253) = UCN1 (U4127 (h), U6631 (r)) = UCN2 (U9507 (m)) = UCN3 (U1008) = Astressin _{2B} (A5227) >> hGRF (G8895), AVP (V9879 , V0377)	UCN1 (U4127 (h), U6631 (r)) = Urotensin I (U7253) > α-helical oCRF(9-41) (C2917) > r/hCRF (C3042)	Urotensin I (U7253) > r/hCRF (C3042) = r/hCRF(1-41)OH = α-helical oCRF(9-41) (C2917) > r/hCRF(6-33) (C0961), > r/hCRF(9-33), > Sauvagine (S3884) >> D-Phe r/hCRF(12-41) > oCRF (C3167) = bCRF (C2671) = Astressin (A4933)
ANTAGONISTS ^c	α-helical oCRF(9-41) (C2917), D-Phe r/hCRF(12-41), Astressin (A4933)	α-helical oCRF(9-41) (C2917), D-Phe r/hCRF(12-41), Astressin (A4933), Astressin- _{2B} (A5227), Antisauvagine-30 (A4727)	α-helical oCRF(9-41) (C2917), D-Phe r/hCRF(12-41), Astressin (A4933), Astressin- _{2B} (A5227), Antisauvagine-30 (A4727)	α-helical oCRF(9-41) (C2917)	Not known
SELECTIVE NON-PEPTIDE ANTAGONISTS	CP 154,526, NBI 27914 (N3911), Antalarmin (A8727), CRA 1000, CRA 1001, DMP 696, DMP 904, NBI 30775/R121919, NBI 35965	Not known	Not known	Not known	Not known
SIGNAL TRANSDUCTION MECHANISM	G _s (increase cAMP)	G _s (increase cAMP)	G _s (increase cAMP)	G _s (increase cAMP)	Not known
RADIOLIGANDS OF CHOICE	[¹²⁵ I]-Tyr ⁰ oCRF, [¹²⁵ I]-Tyr ⁰ r/hCRF, [¹²⁵ I]-Tyr ⁰ Sauvagine, [³ H]-Urocortin	[¹²⁵ I]-Tyr ⁰ Sauvagine, [³ H]-Urocortin, [¹²⁵ I]-Antisauvagine-30	[¹²⁵ I]-Tyr ⁰ Sauvagine, [³ H]-Urocortin, [¹²⁵ I]-Antisauvagine-30	[¹²⁵ I]-Tyr ⁰ Sauvagine, [³ H]-Urocortin, [¹²⁵ I]-Antisauvagine-30	[¹²⁵ I]-Tyr ⁰ r/hCRF, [³ H]-Urocortin

FOOTNOTES

Corticotropin-Releasing Factor Receptors

TISSUE EXPRESSION	Central nervous system, pituitary, testes, gastrointestinal tract, uterus/placenta	Central nervous system, gastrointestinal tract ^d	Skeletal muscle, heart/vasculature, gastrointestinal tract ^d , uterus	Human amygdala	Central nervous system, liver, plasma, placenta, adrenal
PHYSIOLOGICAL FUNCTION	Stimulates release of ACTH, regulates response to stress	Stimulates release of cAMP, regulates food intake	Vasodilation, decreases blood pressure, modulates muscle mass	Stimulates release of cAMP	Reduces CRF activity
DISEASE RELEVANCE^e	Anxiety, depression, irritable bowel syndrome, parturition	Anxiety, eating disorders	Cerebrovascular disease, migraine, congestive heart failure, parturition	Not known	Alzheimer's disease

Abbreviations

Antalarmin: N-Butyl-N-ethyl-[2,5,6,-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine

Antisauvagine-30: (D-Phe¹¹, His¹²)-Sauvagine, Fragment 11-40

Astressin: [D-Phe¹², Nle^{21,38}, Glu³⁰, Lys³³]-Corticotrophin releasing factor fragment 12-41

Astressin 2B: Cyclo(31-34)[D-Phe¹¹, His¹², C(α)MeLeu^{13,39}, Nle¹⁷, Glu³¹, Lys³⁴]Ac-Sauvagine(8-40)

AVP: Arginine vasopressin

CP 154,526: Butyl-ethyl-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine

CRF: Corticotrophin releasing factor

CRF-BP: CRF-Binding Protein

r/hCRF: rat/human CRF

oCRF: ovine CRF

bCRF: bovine CRF

r/hCRF(1-41)OH: Deamidated rat/human corticotrophin releasing factor

D-Phe r/hCRF(12-41): [D-Phe¹², Nle^{21,38}, Ala³²] r/hCRF(12-41)

CRA 1000: 2-(N-(2-Methylthio-4-isopropylphenyl)-N-ethyl-amino-4-(4-(3-fluorophenyl)-1,2,3,6-tetra-hydropyridin-1-yl)-6-methylpyrimidine)

CRA 1001: 2-(N-(2-Bromo-4-isopropylphenyl)-N-ethyl-amino-4-(4-(3-fluorophenyl)-1,2,3,6-tetrahydropyridin-1-yl)-6-methylpyrimidine)

DMP696: 4-(1,3-Dimethoxyprop-2-ylamino)-2,7-dimethyl-8-(2,4-dichlorophenyl)pyrazolo[1,5-a]-1,3,5-triazine

DMP904: 4-(3-Pentylamino)-2,7-dimethyl-8-(2-methyl-4-methoxyphenyl)-pyrazolo-[1,5-a]-pyrimidine

hGRF: Human Growth hormone releasing factor

NBI 27914: 2-Methyl-4-(N-propyl-N-cyclopropanemethylamino)-5-chloro-6-(2,4,6-trichloroanilino)pyrimidine

NBI 30775 / R121919: 3-[6-(Dimethylamino)-4-methyl-3-pyridinyl]-2,5-dimethyl-N,N-dipropylpyrazolo[1,5-a]pyrimidin-7-amine

NBI 35965: (S)-6-Cyclopropylmethyl-2-(2,4-dichloro-phenyl)-7-ethyl-4-methyl-7,8-dihydro-6H-1,3,6,8a-tetraaza-acenaphthylene

UCN1, UCN2, UCN3: Urocortin 1, Urocortin 2 and Urocortin 3.

VIP: Vasoactive intestinal peptide

h: human

o: ovine

m: mouse

r: rat

r/h: rat/human

FOOTNOTES

a Nomenclature as recommended by the NC-IUPHAR Subcommittee on corticotropin-releasing factor receptors, see Hauger, et. al. 2003.

b For the CRF₂ receptor subtype, the recent identification and cloning of Urocortin 3 adds to this subfamily of ligands representing endogenous mammalian peptides that have over 1000-fold selectivity in affinity and functional activity for the CRF₂ receptor over the CRF₁ receptor.

c With the exception of the novel small molecule receptor antagonists being discovered, there are no selective endogenous antagonists for any of these receptor subtypes. Antisauvagine-30 has been reported to have about a 10 - 50-fold selectivity at the CRF₂ versus the CRF₁ receptor subtype, but this is not an endogenous peptide. No selective non-peptide compounds have appeared to date for any of the CRF₂ receptor isoforms or for the CRF binding protein.

d Both CRF_{2(a)} and CRF_{2(b)} receptors are listed where the physiological function described in the literature makes no mention of the specific isoform and is listed as only the CRF₂ receptor.

e To date there have been no clinical proof-of-concept studies completed that demonstrate a clear disease relevance of either activation or blockade of the CRF system. The disease relevance listed is proposed from preclinical and early clinical studies.