

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 recent cloning of multiple receptors for CRF 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 and 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 been designated CRF_{2α}, CRF_{2β} and CRF_{2γ}. The pharmacology and localization of all of these proteins in brain has been well established. The CRF₁ receptor subtype is localized primarily to cortical and cerebellar regions while the CRF_{2α} receptor is localized to subcortical regions including the lateral septum, and paraventricular and ventromedial nuclei of the hypothalamus. The CRF_{2β} receptor is primarily localized to heart, skeletal muscle and brain, to cerebral arterioles and choroid plexus. The CRF_{2γ} receptor has most recently been identified in human amygdala. Expression of these receptors in mammalian cell lines has made possible the identification of non-peptide, high affinity, selective receptor antagonists.

While the natural mammalian ligands oCRF and r/hCRF have high affinity for the CRF₁ receptor subtype, they have lower affinity for the CRF₂ receptor family making them

ineffective labels for CRF₂ receptors. [¹²⁵I]-Sauvagine has been characterized as a high affinity ligand for both the CRF₁ and the CRF₂ receptor subtypes and has been used in both radioligand binding and receptor autoradiographic studies as a tool to aid in the discovery of selective small molecule receptor antagonists. Recently, the discovery of urocortin II, an endogenous mammalian peptide which has high affinity for the CRF₂ receptor and very low affinity for the CRF₁ receptor, has offered new insights into the role and function of the CRF₂ receptor subtype.

Non-peptide CRF₁ receptor antagonists that can specifically and selectively block the CRF₁ receptor subtype have recently been identified. Compounds such as CP 154,526, NBI 27914, DMP 696 and antalarmin all inhibit CRF-stimulation of cAMP or CRF-stimulated ACTH release from cultured rat anterior pituitary cells. Furthermore, 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 attenuate stress-induced elevations in plasma ACTH levels in rats demonstrating that CRF₁ receptors can be blocked in the periphery. Furthermore, peripherally administered CRF₁ receptor antagonists have also been demonstrated to inhibit CRF-induced seizure activity.

The number of potential therapeutic indications for CRF receptor antagonists is increasing at a tremendous rate. While the primary focus for CRF₁ receptor selective antagonists is still in the area of anxiety and depression, animal models have

implicated a beneficial effect of these molecules in the neurodegeneration associated with stroke, the pain associated with various inflammatory responses and their potential utility in irritable bowel syndrome. While selective high-affinity non-peptide molecules have not yet been identified for the CRF₂ receptor subtype, the potential indications for such molecules range from eating disorders to cerebrovascular disease and migraine. It is also tempting to speculate that as more information becomes available through the drug discovery efforts of a variety of pharmaceutical companies or through academic research, that the interaction between the various receptor subtypes may play a unique role in the etiology of various disease states.

Corticotropin-Releasing Factor Receptors

CURRENTLY ACCEPTED NAME ^a	CRF ₁ (human, rat, mouse)	CRF _{2α} (human, rat)	CRF _{2β} (human, rat, mouse)	CRF _{2γ} (human)	CRF-BP (human, rat)
ALTERNATE NAME(S)	CRF-RA (human, rat), PC-CRF (rat, mouse)		CRF-RB (mouse), HM-CRF (mouse)		
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 (C 3042) Urocortin (U 4127 (h) , U 6631 (r))	CRF (C 3042) Urocortin (U 4127 (h) , U 6631 (r)) Urocortin-II	CRF (C 3042) Urocortin (U 4127 (h) , U 6631 (r)) Urocortin-II	CRF (C 3042) Urocortin (U 4127 (h) , U 6631 (r)) Urocortin-II	CRF (C 3042) Urocortin Urocortin-II (U 4127 (h) , U 6631 (r))
PEPTIDE RANK ORDER OF POTENCIES	Sauvagine (S 3884) = Urotensin I (U 7253) = Urocortin (U 4127 (h) , U 6631 (r)) = oCRF (C 3167) = r/hCRF (C 3042) = bCRF (C 2671) > astressin (A 4933) > D-Phe r/h CRF(12-41) > α-helical oCRF(9-41) (C 2917) >> Urocortin II, r/hCRF(6-33) (C 0961), r/hCRF(9-33), r/hCRF(1-41)OH, VIP (V 6130), AVP (V 9879 , V 0377)	Sauvagine (S 3884) = Urotensin I (U 7253) = Urocortin (U 4127 (h) , U 6631 (r)) = Urocortin II (U 9507 (m)) > r/hCRF (C 3042) > oCRF (C 3167) > bCRF (C 2671) > D-Phe r/h CRF(12-41) > α-helical oCRF(9-41) (C 2917) >> r/hCRF(6-33) (C 0961), r/hCRF(9-33), r/hCRF(1-41)OH, VIP (V 6130), AVP (V 9879 , V 0377)	r/hCRF (C 3042) = Sauvagine (S 3884) = Urotensin I (U 7253) >> hGRF (G 8895), AVP (V 9879 , V 0377)	Urocortin (U 4127 (h) , U 6631 (r)) = Urotensin I (U 7253) > α-helical oCRF(9-41) (C 2917), > r/hCRF (C 3042)	Urotensin I (U 7253) > r/hCRF (C 3042) = r/hCRF(1-41)OH = α-helical oCRF(9-41) (C 2917) > r/hCRF(6-33) (C 0961), > r/hCRF(9-33), > Sauvagine (S 3884) >> D-Phe r/h CRF(12-41) > oCRF (C 3167) = bCRF (C 2671) = astressin (A 4933)
ANTAGONISTS ^c	α-helical oCRF(9-41) (C 2917) D-Phe r/hCRF(12-41) Astressin (A 4933)	α-helical oCRF(9-41) (C 2917) D-Phe r/hCRF(12-41) Astressin (A 4933) anti-Sauvagine-30	α-helical oCRF(9-41) (C 2917) D-Phe r/hCRF(12-41) Astressin (A 4933) anti-Sauvagine-30	α-helical oCRF(9-41) (C 2917)	Not Defined
SELECTIVE NON-PEPTIDE ANTAGONISTS	CP 154,526 NBI 27914 Antalarmin CRA 1000, CRA 1001 DMP 696 DMP 904 R121919	None Available	None Available	None Available	None Available
SIGNAL TRANSDUCTION MECHANISM	G _s (increase cAMP)	G _s (increase cAMP)	G _s (increase cAMP)	G _s (increase cAMP)	Not Defined
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]-Tyr ⁰ Sauvagine [³ H]-Urocortin	[¹²⁵ I]-Tyr ⁰ Sauvagine [³ H]-Urocortin	[¹²⁵ I]-Tyr ⁰ r/hCRF [³ H]-Urocortin

ABBREVIATIONS

Antalarmin: N-Butyl-N-ethyl-[2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine
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-BP: CRF-Binding Protein
r/hCRF: rat/human CRF

oCRF: ovine CRF
bCRF: bovine CRF
r/hCRF(1-41)OH: Deamidated rat/human CRF
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
R121919: 3-[6-(Dimethylamino)-4-methyl-3-pyridinyl]-2,5-dimethyl-N,N-dipropylpyrazolo[1,5-a]pyrimidin-7-amine
VIP: Vasoactive intestinal peptide
h: human
m: mouse
r: rat

FOOTNOTES

a Nomenclature as recommended by the NC-IUPHAR Committee on corticotropin-releasing factor receptors, see De Souza et al 1998. With the recent identification and cloning of Urocortin-II, a selective agonist for the CRF₂ receptor, it may be more appropriate to rename the CRF₂ receptor as the Urocortin receptor. The distribution and pharmacological profile now support this change and will be submitted to the NC-IUPHAR Committee for their consideration.

b For the CRF₂ receptor subtype, the recent identification and cloning of Urocortin-II represents the first endogenous mammalian peptide that has 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. Anti sauvagine-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 either the CRF₂ receptor isoforms or for the CRF binding protein.