

# International Union of Pharmacology. XXXVI. Current Status of the Nomenclature for Receptors for Corticotropin-Releasing Factor and Their Ligands

RICHARD L. HAUGER, DIMITRI E. GRIGORIADIS, MARY F. DALLMAN, PAUL M. PLOTSKY, WYLIE W. VALE,  
AND FRANK M. DAUTZENBERG

*Department of Psychiatry and Veterans Affairs Healthcare System, University of California San Diego, La Jolla, California (R.L.H.); Neurocrine Biosciences, Inc., San Diego, California (D.E.G.); Department of Physiology, University of California San Francisco, California (M.F.D.); Stress Neurobiology Laboratory, Department of Psychiatry and Behavioral Sciences, Emory University, Atlanta, Georgia (P.M.P.); Clayton Foundation Laboratories for Peptide Biology and Laboratory of Neuronal Structure and Function, Salk Institute for Biological Studies, La Jolla, California (W.W.V.); c./o. Axovan. Ltd., Allschwil-Switzerland (F.M.D.)*

Abstract .....	21
I. Introduction .....	21
II. The corticotropin-releasing factor type 1 receptor .....	22
III. The corticotropin-releasing factor type 2 receptor .....	23
IV. Proposed nomenclature .....	24
V. Unresolved issues .....	25
Acknowledgments .....	25
References .....	25

**Abstract**— Receptors for corticotropin-releasing factor (CRF) are members of a family of G protein-coupled receptors (“Family B”) that respond to a variety of structurally dissimilar releasing factors, neuropeptides, and hormones (including secretin, growth hormone-releasing factor, calcitonin, parathyroid hormone, pituitary adenylate cyclase-activating polypeptide, and vasoactive intestinal polypeptide) and signal through the cyclic AMP and/or calcium pathways. To

date, three genes encoding additional CRF-like peptides (urocortins) have been identified in mammals. The urocortins and CRF bind with differential ligand selectivity at the two mammalian CRF receptors. This report was prepared by the International Union of Pharmacology Subcommittee on CRF Receptors, to summarize the current state of CRF receptor biology and to propose changes in the classification and nomenclature of CRF ligands and receptors.

## I. Introduction

In 1981, the 41-amino acid corticotropin-releasing factor (CRF<sup>1</sup>) peptide was isolated from ovine hypothalamus (Vale et al., 1981). Initially, the action of CRF appeared to be restricted to regulating ACTH secretion by pituitary corticotrope cells (Vale et al., 1981; Dunn and Berridge 1990; Hauger and Dautzenberg, 1999; Smagin et al., 2001). The central distribution of CRF pathways, however, suggested that CRF’s function extended far beyond the classical action of a hormone

(Swanson et al., 1983; De Souza et al., 1984; Wynn et al., 1984; Vale et al., 1997; Arborelius et al., 1999; Heinrichs and De Souza 1999; Dautzenberg et al., 2001a). Because CRF was shown to generate neuroendocrine, autonomic, and behavioral stress responses, it was hypothesized that CRF contributed to the development of stress and affective disorders by over-activating its receptors expressed in various brain neurons in neocortex, the amygdala and its extended neurocircuits, and brainstem nuclei.

Urocortin, a second mammalian CRF-like peptide was identified after two novel CRF-like peptides, urotensin I (Lederis et al., 1982) and sauvagine (Montecucchi and Henschen, 1981), were discovered in fish and amphibian species in addition to CRF (Okawara et al., 1988; Stenzel-Poore et al., 1992). Human, sheep, rat, and mouse urocortin possess a 40-amino acid sequence (Vaughan et al., 1995; Donaldson et al., 1996; Zhao et al., 1998; Cepoi et al., 1999) and a high degree of homology with fish

Address correspondence to: Dr. Frank M. Dautzenberg, c./o. Axovan Ltd., Gewerbestrasse 16, CH-4070 Allschwil, Switzerland. E-mail: frank.dautzenberg@t-online.de

<sup>1</sup> CRF, corticotropin-releasing factor; IUPHAR, International Union of Pharmacology; ACTH, adrenocorticotropin; CRH, corticotropin-releasing hormone; kb, kilobase(s).

Article, publication date, and citation information can be found at <http://pharmrev.aspetjournals.org>

DOI: 10.1124/pr.55.1.3

urotensin I. Although the Edinger-Westphal locus, the hypothalamus, and a small population of forebrain neurons express substantial levels of urocortin (Bittencourt et al., 1999), urocortin is more broadly expressed in the periphery, especially in the pituitary, gastrointestinal tract, testis, cardiac myocytes, thymus, spleen, and kidney (Kageyama et al., 1999).

Very recently, two novel isoforms of urocortin, urocortin 2 and urocortin 3 (Lewis et al., 2001; Reyes et al., 2001), were cloned at the Salk Institute from human and mouse cDNA libraries. At the same time, another group identified two similar peptides, which they named stresscopin (which is homologous with urocortin 3) and stresscopin-related peptide (which is homologous with urocortin 2) (Hsu and Hsueh, 2001). Urocortin 2 (stresscopin-related peptide) and urocortin 3 (stresscopin) are discretely expressed in the central nervous system with a pattern distinct from the known CRF and urocortin pathways (Hsu and Hsueh, 2001; Lewis et al., 2001; Reyes et al., 2001). Furthermore, the central distribution of urocortin 1-, urocortin 3-, and CRF<sub>2</sub> receptor-expressing neurons suggests that urocortin 1 may serve as the major CRF<sub>2</sub> receptor ligand in the hindbrain whereas urocortin 3 may serve as the major CRF<sub>2</sub> receptor ligand in the forebrain. Urocortin 2 or a novel endogenous ligand may signal at CRF<sub>2</sub> receptors expressed in certain brain regions lacking urocortin 1 or urocortin 3 innervations (e.g., the hippocampus and certain regions of the cerebral cortex). Because neither CRF<sub>1</sub> nor CRF<sub>2</sub> receptors have yet been identified in the locus coeruleus, central nucleus of the amygdala, and several other stress-sensitive brain structures, it is possible that a novel CRF receptor may eventually be cloned (Hsu and Hsueh, 2001; Li et al., 2002). In the periphery, urocortin 2 mRNA is detected in the heart, adrenal gland, and peripheral blood cells (Hsu and Hsueh, 2001; Reyes et al., 2001). The highest peripheral levels of urocortin 3 mRNA expression have been detected in the gastrointestinal tract, muscle, adrenal gland, and skin (Hsu and Hsueh, 2001; Lewis et al., 2001). Because urocortin 2 and urocortin 3 have been identified by molecular cloning strategies (Hsu and Hsueh, 2001; Lewis et al., 2001; Reyes et al., 2001), their exact size has not been established yet. The structure of both precursor genes appears to predict 38-amino acid mature peptides (Lewis et al., 2001; Reyes et al., 2001) although one group (Hsu and Hsueh, 2001) postulated the existence of N-terminally extended peptides 40 (urocortin 3) and 43 (urocortin 2) amino acids in length. However, because the human and mouse homologues of both precursors are less conserved in the extended N terminus than in the remaining sequence, it seems more likely that urocortin 2 and urocortin 3 exist as 38-amino acid peptides. Furthermore, the 38- and the 40-/43-amino acid versions of both ligands possess similar pharmacological potencies. Because CRF ligands rapidly lose agonistic potency upon N-terminal truncation (Rivier et al., 1984; Brauns

et al., 2002) the pharmacological data also speak in favor of the 38-amino acid variants for urocortin 2 and urocortin 3. This issue will not be conclusively resolved until endogenous forms of these two urocortin peptides are isolated in various species. Like CRF (Vale et al., 1981) and urocortin 1 (Vaughan et al., 1995), urocortin 2 and urocortin 3 possess biological activity only when they are C-terminally amidated (Hsu and Hsueh, 2001). Only 4 amino acids are completely conserved among CRF peptides (Fig. 1). Therefore, secondary structure rather than linear sequence homology most likely determines differences in biological activity of the members of the CRF peptide family (Hsu and Hsueh, 2001; Lewis et al., 2001; Reyes et al., 2001; Dautzenberg and Hauger, 2002).

## II. The Corticotropin-Releasing Factor Type 1 Receptor

The CRF<sub>1</sub> receptor, a 415–446 amino acid polypeptide, has been cloned from a variety of species including man (Chen et al., 1993; Vita et al., 1993), tree shrew (Palchadhuri et al., 1998), mouse (Vita et al., 1993), rat (Chang et al., 1993; Perrin et al., 1993), sheep (Myers et al., 1998), chicken (Yu et al., 1996), frog (Dautzenberg et al., 1997), and fish (Arai et al., 2001; Pohl et al., 2001). Although a larger number of splice variants of the CRF<sub>1</sub> receptor cDNA have been identified (Chang et al., 1993; Chen et al., 1993; Ross et al., 1994; Myers et al., 1998; Grammatopoulos et al., 1999) (Fig. 2), they have not been shown to encode functional receptors *in vivo* due to their low binding affinity or lack of activation in recombinant systems (reviewed in Dautzenberg et al., 2001a). The CRF<sub>1</sub> receptor is abundantly expressed in the central nervous system with major expression sites in cortex, cerebellum, hippocampus, amygdala, olfactory bulb, and pituitary (Potter et al., 1994; Chalmers et al., 1996; Palchadhuri et al., 1998). In the periphery, CRF<sub>1</sub> receptor mRNA is expressed at low levels in the skin, ovary, testis, and adrenal gland (Vita et al., 1993; Nappi and Rivest, 1995; Palchadhuri et al., 1998).

Binding and functional studies using cell lines recombinantly or endogenously expressing CRF<sub>1</sub> receptors revealed a distinct ligand-selective profile whereby human and ovine CRF, urocortin 1, urotensin I, and sauvagine all bind with high affinity to the mammalian CRF<sub>1</sub> receptor and activate the cyclic AMP signaling pathway

Peptide	Sequence	Length	Identity(%)
hCRF	SEEPPI <b>SLD</b> LT <b>PHLL</b> REVLEMARAEQLAQQ <b>PHSN</b> NRKLMLEII	41	100
oCRF	SQEPPI <b>SLD</b> LT <b>PHLL</b> REVLEMTKADQLAEO <b>PHSN</b> NRKLLDIA	41	83
hUCN 1	DNPSLS <b>SLD</b> LT <b>PHLL</b> R <b>TLE</b> ELARTQSQRERAEONRIIFDSV	40	43
hUCN 2	IVLSL <b>SLD</b> VPTIGLLQILLEQARARAAREQATTNARILARV	38	34
mUCN 2	VILSL <b>SLD</b> VPIGLLRILLEQARYKAARNQAA <b>TNA</b> QILAHV	38	34
hUCN 3	FTLSL <b>SLD</b> VPTNIMNLLFNIAKAKNLRACAA <b>NA</b> HLMAQI	38	32
mUCN 3	FTLSL <b>SLD</b> VPTNIMNLLFNIDKAKNLRACAA <b>NA</b> QLMAQI	38	26

FIG 1. Alignment of the members of the CRF peptide family. The amino acids that are homologous between the CRF peptides are boxed. h, human; m, mouse; o, ovine; UCN 1, urocortin 1; UCN 2, urocortin 2; UCN 3, urocortin 3.

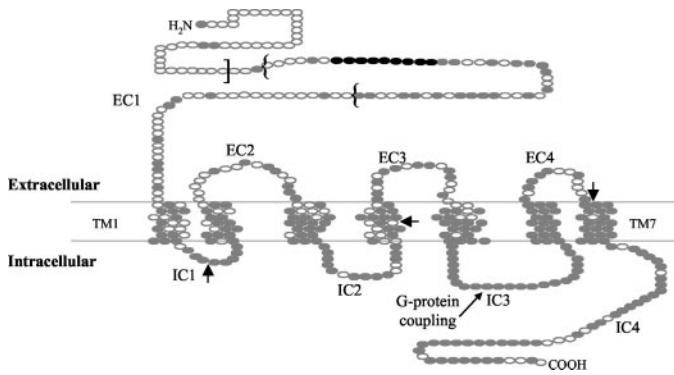


FIG 2. Two-dimensional structure of the human CRF<sub>1</sub> and CRF<sub>2</sub> receptors. Identical amino acids between both receptors are represented as filled circles whereas divergent residues are shown as open circles. The arrows indicate sites for insertion or deletion of exons in nonfunctional variants of the CRF<sub>1</sub> and CRF<sub>2</sub> receptor (Chen et al., 1993; Myers et al., 1998; Grammatopoulos et al., 1999; Miyata et al., 1999). The symbols { and } indicate the deletion of a 40-amino acid exon in a nonfunctional splice variant of the human CRF<sub>1</sub> receptor (Ross et al., 1994) whereas the symbol | represents the common splice site for the three CRF<sub>2</sub> variants CRF<sub>2(a)</sub>, CRF<sub>2(b)</sub>, and CRF<sub>2(c)</sub>.

(Donaldson et al., 1996; Dautzenberg et al., 1997, 2001b; Perrin et al., 1999). In contrast, urocortin 2 and urocortin 3 do not bind to or activate CRF<sub>1</sub> receptors (Hsu and Hsueh, 2001; Lewis et al., 2001; Reyes et al., 2001). Therefore, CRF and urocortin 1 can be classified as the endogenous ligands for mammalian CRF<sub>1</sub> receptors (Fig. 3).

### III. The Corticotropin-Releasing Factor Type 2 Receptor

Complementary DNAs for the CRF<sub>2</sub> receptor have been isolated from man (Liaw et al., 1996; Valdenaire et

al., 1997; Kostich et al., 1998), tree shrew (Palchauthuri et al., 1999), rat (Lovenberg et al., 1995b), mouse (Kishimoto et al., 1995; Perrin et al., 1995; Stenzel et al., 1995), frog (Dautzenberg et al., 1997), and fish (Arai et al., 2001; Pohl et al., 2001). Three functional splice variants (Lovenberg et al., 1995b; Kostich et al., 1998) and a truncation variant (Miyata et al., 1999) have been identified for the mammalian CRF<sub>2</sub> receptor. The CRF<sub>2(a)</sub> receptor variant is only expressed in nonmammalian species (Dautzenberg et al., 1997; Arai et al., 2001; Pohl et al., 2001), whereas the 430–438 amino acid CRF<sub>2(b)</sub> receptor and the CRF<sub>2(a)</sub> receptor are both expressed in mammals (Kishimoto et al., 1995; Lovenberg et al., 1995b; Perrin et al., 1995; Stenzel et al., 1995; Valdenaire et al., 1997; Palchauthuri et al., 1999). Expression of the 397-amino acid CRF<sub>2(c)</sub> receptor has only been detected in limbic regions of the human central nervous system (Kostich et al., 1998). Splicing of the CRF<sub>2</sub> receptor variants occurs at the extreme 5' terminus of the receptor gene and reflects usage of different promoters in man. The hCRF<sub>2</sub> gene, which is located on chromosome 7p14-15, is ~50 kb in size and contains 15 exons (Dautzenberg et al., 2000). The first four exons give rise to the different 5'-ends of the splice variants hCRF<sub>2(a)</sub>, hCRF<sub>2(b)</sub> and hCRF<sub>2(c)</sub>, respectively; exons 5 to 15 form the common parts of the various hCRF<sub>2</sub> splice variants. Exons 1 and 2, which are separated by ~10.5 kb intronic sequence encode the CRF<sub>2(b)</sub>-specific part, followed by the CRF<sub>2(c)</sub> and CRF<sub>2(a)</sub> exons (Dautzenberg et al., 2000).

In rodents, CRF<sub>2(a)</sub> receptor mRNA is expressed primarily in brain neurons whereas CRF<sub>2(b)</sub> receptor mRNA is detected in non-neuronal brain structures such

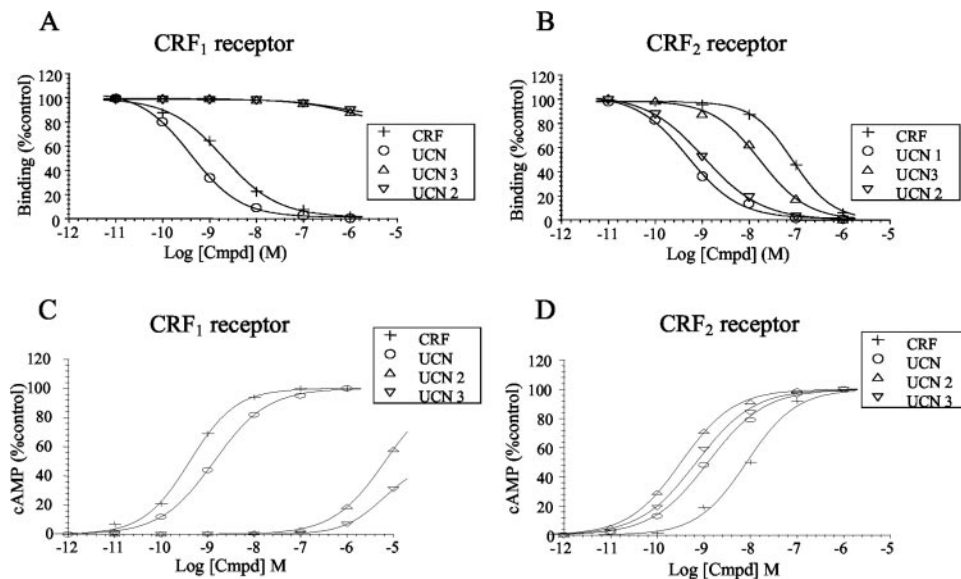


FIG 3. Pharmacological properties of the four mammalian CRF agonists CRF, urocortin 1, urocortin 2, and urocortin 3 at the human CRF<sub>1</sub> and CRF<sub>2</sub> receptors. Binding of the four natural agonists to the CRF<sub>1</sub> (A) and CRF<sub>2</sub> (B) receptors reveals a distinct profile for each ligand with urocortin 1 being a high-affinity ligand to both receptors and CRF being a high affinity ligand to the CRF<sub>1</sub> and a low-affinity ligand to the CRF<sub>2</sub> receptor. Urocortin 2 and urocortin 3, however, only bind to the CRF<sub>2</sub> receptor. Similar findings are observed in cAMP stimulation studies with recombinant receptors (C and D). In contrast to the binding studies, however, a very weak agonistic potency (>1 μM) is observed for urocortin 2 and urocortin 3 at the CRF<sub>1</sub> receptor (C).



as the choroid plexus cerebral arterioles and peripheral tissues (Lovenberg et al., 1995a). The CRF<sub>2(a)</sub> receptor is the dominant CRF<sub>2</sub> receptor splice variant expressed in the mammalian brain. Central CRF<sub>2(a)</sub> receptors are expressed in a discrete pattern with highest densities in the lateral septum, ventromedial hypothalamus, cortical nucleus of the amygdala, dorsal raphe, nucleus of the solitary tract, and the choroid plexus; whereas, a widespread but discrete expression of CRF<sub>1</sub> receptors is found in neocortex and the amygdala and its extended neurocircuits (Bittencourt et al., 1999; Li et al., 2002). In humans and tree shrews, CRF<sub>2(a)</sub> receptor mRNA has also been detected in the brainstem, olfactory bulbs, cortex, cerebellum, retina, and pituitary (Palchadhuri et al., 1999; Sanchez et al., 1999). Because CRF<sub>2(b)</sub> receptor mRNA can be detected in neuronal structures such as retina and cerebellum, the distribution of these two splice variants may overlap in primates and primate-like animals. In the periphery, substantial expression of CRF<sub>2</sub> receptor can be found in the heart, skeletal muscle, vasculature, and gastrointestinal tract. The CRF<sub>2(a)</sub> receptor is the major splice variant found in the peripheral tissues of humans (e.g., heart and skeletal muscle) (Valdenaire et al., 1997; Kostich et al., 1998), whereas the CRF<sub>2(b)</sub> splice variant is the CRF<sub>2</sub> receptor peripherally expressed in rodents. The main expression sites for the rodent CRF<sub>2(b)</sub> receptor have been reported for heart, lung, skeletal muscle, gastrointestinal tract, testis, and ovaries (Lovenberg et al., 1995a; Palchadhuri et al., 1999).

Pharmacological characterization of the CRF<sub>2</sub> receptor splice variants revealed no major differences between CRF<sub>2(a)</sub>, CRF<sub>2(b)</sub>, and CRF<sub>2(c)</sub> receptors (Donaldson et al., 1996; Kostich et al., 1998; Palchadhuri et al., 1999). However, the binding profiles of these three CRF<sub>2</sub> receptors strongly diverge from the binding profile of the CRF<sub>1</sub> receptor (Donaldson et al., 1996; Perrin et al., 1999; Dautzenberg et al., 2001b; Hsu and Hsueh, 2001; Lewis et al., 2001; Reyes et al., 2001). The nonmammalian CRF peptides urotensin I and sauvagine and the mammalian peptides urocortin 1, urocortin 2, and urocortin 3 generally bind with up to 100-fold higher affinities to the CRF<sub>2</sub> receptor than species homologues of CRF (Fig. 3B). In agreement with the binding data, a similar rank order of potency is typically observed when stimulation of intracellular cyclic AMP accumulation is measured (Donaldson et al., 1996; Dautzenberg et al., 2001b; Hsu and Hsueh, 2001; Lewis et al., 2001; Reyes et al., 2001) (Fig. 3D). Therefore, currently, urocortin 2 and urocortin 3 are generally considered to represent the endogenous ligands for mammalian CRF<sub>2</sub> receptor variants, whereas urocortin 1 is thought to be an endogenous ligand for both the CRF<sub>1</sub> and CRF<sub>2</sub> receptors.

#### IV. Proposed Nomenclature

Early clinical neuroendocrine studies, particularly those directed at investigating the role of CRF in regu-

lating the hypothalamic-pituitary-adrenal axis, defined this peptide's function to be a stimulator of ACTH secretion. Accordingly, the term "corticotropin-releasing hormone" gained acceptance in the neuroendocrine literature. However, ample evidence has accumulated over the past two decades demonstrating that CRF's physiological function extends far beyond the biology of a hormone. In fact, CRF most likely plays a role in immune, neurodegenerative, neuropsychiatric, and gastrointestinal disorders. Thus, the term "corticotropin-releasing factor" more appropriately designates the function of this peptide. It is recommended that CRF rather than corticotropin-releasing hormone (CRH) should be used in keeping with the nomenclature for other important factors (i.e., transforming growth factor and brain-derived neurotrophic factor) that exhibit a multiplicity of biological actions.

The three-dimensional structure, CRF<sub>2</sub> receptor binding profile, and biological actions of urocortin 2 and urocortin 3 are similar to each other and to urocortin 1 (see Hsu and Hsueh, 2001; Lewis et al., 2001; Reyes et al., 2001; Dautzenberg and Hauger, 2002). These novel ligands should therefore retain the following designations: urocortin 2 and urocortin 3. Stresscopin, which has recently been used to designate the peptide with urocortin 2's sequence, implies its role is to mediate an organism's "coping" with stress. Activation of central CRF<sub>2</sub> receptors can produce anxiogenesis or anxiolysis depending on the brain site (Reul and Holsboer, 2002). Thus, the term "stresscopin" (Hsu and Hsueh, 2001) only covers one aspect of the behavioral response mediated by brain CRF<sub>2</sub> receptor signaling. Therefore, the urocortin 2 and urocortin 3 should be used in place of the terms stresscopin and stresscopin-related peptide, respectively. Finally, since the urocortin family contains three members, urocortin 1 will replace the earlier generic term "urocortin". Table 1 summarizes all of the recommended changes for the nomenclature of CRF peptides.

A revised nomenclature for CRF receptors is summarized in Table 2. Although several alternative terminologies such as CRH1, CRFR1 or CRF-R1 have been used to designate the CRF<sub>1</sub> receptor, the term CRF<sub>1</sub> receptor should be utilized. Because the CRF<sub>2</sub> receptor is highly selective for urocortin 1 over CRF, renaming the CRF<sub>2</sub> receptor as the urocortin receptor was considered. However, urocortin 1 binds equally well to the CRF<sub>1</sub> and CRF<sub>2</sub> receptors. Therefore, redesignating the CRF<sub>2</sub> receptor as the urocortin receptor fails to distinguish the biology of the two receptors. Therefore, the term CRF<sub>2</sub> receptor should be used for the time being to maintain clarity (Table 2). As new insight into the normal and pathophysiological actions of the CRF<sub>2</sub> receptor subtypes is gained, and as species variations and the behavioral roles of the CRF<sub>2</sub> receptor subtypes become understood, the naming of this CRF receptor may require future revisions. In addition, in accordance with IUPHAR convention, CRF receptor splice variants

TABLE 1  
Nomenclature of the members of the CRF ligand and receptor family

Names in Current Usage	IUPHAR Consensus	HUGO Gene Name	Chromosomal Localization	SWISS-PROT Accession No.
Corticotropin-releasing factor; corticotropin releasing hormone	CRF	CRH	Human 8q13.1	Human P06850
Urocortin	Urocortin 1	UCN	Mouse 3A2 Human 2p23.3 Mouse 5B1	Rat P01143 Human P55089 Mouse P81615 Rat P55090
Urocortin II; urocortin-related peptide; stresscopin-related peptide	Urocortin 2		Human 3p21.31	Human Q96RP3 Mouse Q99ML8 Rat Q91WW1
Urocortin III; stresscopin	Urocortin 3			Human Q969E3 Mouse Q924A4

TABLE 2  
Nomenclature of CRF receptors

Frequently Used Names	IUPHAR Consensus	IUPHAR Receptor Code	Gene Name	Chromosomal Localization	SWISS-PROT Accession No.
CRF <sub>1</sub> ; CRH <sub>1</sub> ; CRF-R1; CRH-R1; CRFR1; CRHR1; CRFR1 $\alpha$	CRF <sub>1</sub>	2.2:CRF:1:CRF1:HUMAN:00 2.2:CRF:1:CRF1:MOUSE:00 2.2:CRF:1:CRF1:RAT:00	CRHR1 Crhr	17q21.31 11E1	P34998 P35347 P35353
CRF <sub>2</sub> ; CRH <sub>2</sub> ; CRF-R2; CRH-R2; CRFR2; CRHR2	CRF <sub>2</sub>	2.2:CRF:2:CRF2:HUMAN 2.2:CRF:2:CRF2:MOUSE 2.2:CRF:2:CRF2:RAT	CRHR2 Crhr2	7p14.3 6B3	Q13324 Q60748 P47866
CRF <sub>2(a)</sub> ; CRH <sub>2(a)</sub> ; CRF <sub>2(a)</sub> ; CRH <sub>2(a)</sub> ; CRF-R2 $\alpha$ ; CRH-R2 $\alpha$ ; CRFR2 $\alpha$ ; CRHR2 $\alpha$	CRF <sub>2(a)</sub>	2.2:CRF:2:CRF2:HUMAN:01 2.2:CRF:2:CRF2:RAT:01			— <sup>a</sup> — <sup>b</sup>
CRF <sub>2(b)</sub> ; CRH <sub>2(b)</sub> ; CRF <sub>2(b)</sub> ; CRH <sub>2(b)</sub> ; CRF-R2 $\beta$ ; CRH-R2 $\beta$ ; CRFR2 $\beta$ ; CRHR2 $\beta$	CRF <sub>2(b)</sub>	2.2:CRF:2:CRF2:HUMAN:02 2.2:CRF:2:CRF2:MOUSE:01 2.2:CRF:2:CRF2:RAT:02			— <sup>c</sup> — <sup>d</sup> — <sup>b</sup>
CRF <sub>2(c)</sub> ; CRH <sub>2(c)</sub> ; CRF <sub>2(c)</sub> ; CRH <sub>2(c)</sub> ; CRF-R2 $\gamma$ ; CRH-R2 $\gamma$ ; CRFR2 $\gamma$ ; CRHR2 $\gamma$	CRF <sub>2(c)</sub>	2.2:CRF:2:CRF2:HUMAN:03			— <sup>e</sup>

<sup>a</sup> Liaw et al., 1996; <sup>b</sup> Lovenberg et al., 1995b; <sup>c</sup> Valdenaire et al., 1997; <sup>d</sup> Perrin et al., 1995; <sup>e</sup> Kostich et al., 1998.

should be listed alphabetically using Roman rather than Greek letters as have appeared in the current literature (Humphrey and Barnard, 1998). Thus, the three CRF<sub>2</sub> receptor splice variants will be designated as CRF<sub>2(a)</sub>, CRF<sub>2(b)</sub>, and CRF<sub>2(c)</sub>. Finally, as novel CRF<sub>1</sub> and CRF<sub>2</sub> splice variants become identified, they will only be classified as formal CRF receptors if they encode physiologically functional receptor proteins but not simply polymerase chain reaction products. Numerous low-affinity or nonfunctional CRF receptor variants possess an incomplete structure due to either exon deletions or insertions, which mostly occur in a single species (reviewed in Dautzenberg et al., 2001a).

### V. Unresolved Issues

Recently a third CRF receptor, termed CRF<sub>3</sub>, was cloned from catfish (Arai et al., 2001). The catfish CRF<sub>3</sub> receptor was not detected in salmon (Pohl et al., 2001). The catfish CRF<sub>1</sub> and CRF<sub>3</sub> receptors are highly homologous. Interestingly, CRF<sub>3</sub> receptor expression is restricted to the catfish pituitary, a tissue that normally expresses CRF<sub>1</sub> receptors in other species (Arai et al., 2001). Species homologues for this receptor may not exist.

Human urocortin 2 lacks the standard consensus site required for proteolytic cleavage and C-terminal amidation, which is a prerequisite for biological potency (re-

viewed in Dautzenberg and Hauger, 2002). Therefore, human urocortin 2 may not be processed into a biologically active peptide in vivo (Hsu and Hsueh, 2001; Reyes et al., 2001). The isolation of the urocortin 2 peptide from native human tissues would resolve this issue.

*Acknowledgments.* We thank Profs. A. J. Harmar and M. Spedding for liaison with the IUPHAR Committee on Receptor Nomenclature and Drug Classification (NC-IUPHAR).

### References

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**:446–454.

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.

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.

Brauns O, Brauns S, Zimmermann B, Jahn O, and Spiess J (2002) Differential responsiveness of CRF receptor subtypes to N-terminal truncation of peptidic ligands. *Peptides* **23**:881–888.

Cepoi D, Sutton S, Arias C, Sawchenko P, and Vale WW (1999) Ovine genomic urocortin: cloning, pharmacological characterization and distribution of central mRNA. *Mol Brain Res* **68**:109–118.

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**:166–172.

Chang CP, Pearce RV II, 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**:1187–1195.

Chen R, Lewis KA, Perrin MH, and Vale WW (1993) Expression cloning of a human corticotropin-releasing factor receptor. *Proc Natl Acad Sci USA* **90**:8967–8971.

Dautzenberg FM, Dietrich K, Palchadhuri MR, and Spiess J (1997) Identification of two corticotropin-releasing factor receptors with high ligand selectivity from *Xe-*

- nopus laevis*: unusual pharmacology of the type 1 receptor. *J Neurochem* **69**:1640–1649.
- Dautzenberg FM and Hauger RL (2002) The CRF peptide family and their receptors: yet more partners discovered. *Trends Pharmacol Sci* **23**:71–77.
- Dautzenberg FM, Huber G, Higelin J, Py-Lang G, and Kilpatrick GJ (2000) Evidence for the abundant expression of Arginine 185 containing human CRF<sub>2a</sub> receptors and the role of position 185 for receptor-ligand selectivity. *Neuropharmacology* **39**:1368–1376.
- Dautzenberg FM, Kilpatrick GJ, Hauger RL, and Moreau J-L (2001a) Molecular biology of the CRH receptors – in the mood. *Peptides* **22**:753–760.
- Dautzenberg FM, Py-Lang G, Higelin J, Fischer C, Wright MB, and Huber G (2001b) Different binding modes of amphibian and human CRF type 1 and type 2 receptors: evidence for evolutionary differences. *J Pharmacol Exp Ther* **296**:113–120.
- 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 (Wash DC)* **224**:1449–1451.
- Donaldson C, Sutton S, Perrin MH, Corrigan AZ, Lewis KA, Rivier J, Vaughan JM, and Vale WW (1996) Cloning and characterization of human urocortin. *Endocrinology* **137**:2167–2170.
- Dunn AJ and Berridge CW (1990) Physiological and behavioral responses of corticotropin releasing factor administration: is CRF a mediator of anxiety or stress responses? *Brain Res Rev* **15**:71–100.
- Grammatopoulos DK, Dai Y, Randeava HS, Levine MA, Karteris E, Easton AJ, and Hillhouse EW (1999) A novel spliced variant of the type 1 corticotropin-releasing hormone receptor with a deletion in the seventh transmembrane domain present in the human pregnant term myometrium and fetal membranes. *Mol Endocrinol* **13**:2189–2202.
- Hauger RL and Dautzenberg FM (1999) Regulation of the stress response by corticotropin-releasing factor receptors, in *Neuroendocrinology in Physiology and Medicine* (Conn PM, Freedman ME, eds), pp 261–286, Humana Press, Inc., Totowa, NJ.
- Heinrichs SC and De Souza EB (1999) Corticotropin-releasing factor antagonists, binding-protein and receptors: implications for central nervous system disorders. *Bailliere's Best Pract Res Clin Rheumatol* **13**:541–554.
- Humphrey PPA and Barnard EA (1998) International Union of Pharmacology. XIX. The IUPHAR receptor code: a proposal for an alphanumeric classification system. *Pharmacol Rev* **50**:271–277.
- Hsu SY and Hsueh AJW (2001) Human stresscopin and stresscopin-related peptide are selective ligands for the type 2 corticotropin-releasing hormone receptor. *Nat Med* **7**:605–611.
- 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**:5651–5658.
- Kishimoto T, Pearce RV II, Lin CR, and Rosenfeld MG (1995) A sauvagine/corticotropin-releasing factor receptor expressed in heart and skeletal muscle. *Proc Natl Acad Sci USA* **92**:1108–1112.
- Kostich WA, Chen A, Sperle K, and Largent BL (1998) Molecular identification and analysis of a novel human corticotropin-releasing factor (CRF) receptor: the CRF<sub>2γ</sub> receptor. *Mol Endocrinol* **12**:1077–1085.
- Lederis K, Letter A, McMaster D, and Moore G (1982) Complete amino acid sequence of urotensin-I, a hypotensive and corticotropin-releasing neuropeptide from *Catostomus*. *Science (Wash DC)* **218**:162–164.
- Lewis K, Li C, Perrin MH, Bount A, Kunitake K, Donaldson C, Vaughan J, Reyes TM, Gulyas J, Fischer W, Bilezikjian L, Rivier J, Sawchenko PE, and Vale WW (2001) *Proc Natl Acad Sci USA* **98**:7570–7575.
- Li C, Vaughan J, Sawchenko PE, and Vale WW (2002) Urocortin III-immunoreactive projections in rat brain: partial overlap with sites of type 2 corticotropin-releasing factor receptor expression. *J Neurosci* **22**:991–1001.
- 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**:72–77.
- Lovenberg TW, Chalmers DT, Liu C, and De Souza EB (1995a) CRF<sub>2α</sub> and CRF<sub>2β</sub> receptor mRNAs are differentially distributed between the rat central nervous system and peripheral tissues. *Endocrinology* **136**:4139–4142.
- Lovenberg TW, Liaw CW, Grigoriadis DE, Clevenger W, Chalmers DT, De Souza EB, and Oltersdorf T (1995b) Cloning and characterization of a functionally distinct corticotropin releasing factor receptor subtype from rat brain. *Proc Natl Acad Sci USA* **92**:836–840.
- Miyata I, Shiota C, Ikeda Y, Oshida Y, Chaki S, Okuyama S, and Inagami T (1999) Cloning and characterization of a short variant of the corticotropin-releasing factor receptor subtype from rat amygdala. *Biochem Biophys Res Commun* **256**:692–696.
- 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 Peptide Protein Res* **18**:113–120.
- Myers EA, 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.
- 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**:1417–1428.
- 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 USA* **85**:8439–8443.
- Palchadhuri 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**:419–428.
- Palchadhuri 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.
- Perrin M, Donaldson C, Chen R, Blunt A, Berggren T, Bilezikjian L, Sawchenko P and Vale W (1995) Identification of a second corticotropin-releasing factor receptor gene and characterization of a cDNA expressed in heart. *Proc Natl Acad Sci USA* **92**:2969–2973.
- 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**:3058–3061.
- 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**:729–734.
- 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.
- 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 USA* **91**:8777–8781.
- Reul JM and Holsboer F (2002) Corticotropin-releasing factor receptors 1 and 2 in anxiety and depression. *Curr Opin Pharmacol* **2**:23–33.
- Reyes TM, Lewis K, Perrin MH, Kunitake KS, Vaughan J, Arias CA, Hogenesch JS, Gulyas J, Rivier J, Vale WW, and Sawchenko PE (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 USA* **98**:2843–2848.
- Rivier J, Rivier C, and Vale W (1984) Synthetic competitive antagonists of corticotropin-releasing factor: effect on ACTH secretion in the rat. *Science (Wash DC)* **224**:889–891.
- Ross PC, Kostas CM, and Ramabhadran TV (1994) A variant of the human corticotropin-releasing factor (CRF) receptor: cloning, expression and pharmacology. *Biochem Biophys Res Commun* **205**:1836–1842.
- Sanchez 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**:365–377.
- Smagin GN, Heinrichs SC, and Dunn AJ (2001) The role of CRH in behavioral responses to stress. *Peptides* **22**:713–724.
- 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**:637–645.
- 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**:1716–1724.
- 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**:165–186.
- Valdenaire O, Giller T, Breu V, Gottowik J, and Kilpatrick G (1997) A new functional isoform of the human CRF<sub>2</sub> receptor for corticotropin-releasing factor. *Biochim Biophys Acta* **1352**:129–132.
- 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 (Wash DC)* **213**:1394–1397.
- Vale W, Vaughan J, and Perrin M (1997) Corticotropin-releasing factor (CRF) family of ligands and their receptors. *The Endocrinologist* **7**:S3–S9.
- Vaughan J, Donaldson C, Bittencourt J, Perrin MH, Lewis K, Sutton S, Chan R, Turnbull AV, Lovejoy D, Rivier C, Rivier J, Sawchenko PE and Vale W (1995) Urocortin, a mammalian neuropeptide related to fish urotensin I and to corticotropin-releasing factor. *Nature (Lond)* **378**:287–292.
- 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 and human brain corticotropin releasing factor receptors. *FEBS Lett* **335**:1–5.
- 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.
- 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**:192–197.
- Zhao L, Donaldson CJ, Smith GW, and Vale WW (1998) The structure of the mouse and human urocortin genes. *Genomics* **50**:23–33.