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Review

# The role of CRF receptors in anxiety and depression: Implications of the novel $CRF_1$ agonist cortagine

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**Abstract**

Corticotropin-releasing factor (CRF), a 41 amino acid peptide exhibits its actions through two pharmacologically distinct CRF receptor subtypes $CRF_1$ and $CRF_2$. Regulation of the relative contribution of the two CRF receptors to central CRF activity may be essential in coordinating physiological responses to stress. To facilitate the analysis of their differential involvement, we recently developed a $CRF_1$-selective agonist cortagine by synthesis of chimeric peptides derived from human/rat CRF, ovine CRF, and sauvagine. Cortagine was analyzed in behavioral experiments using male wild type and $CRF_2$-deficient C57BL/6J mice for its action on anxiety- and depression-like behaviors. In contrast to the current hypothesis that increased $CRF_1$ activity facilitates the expression of anxiety- and depression-like behavior, cortagine combines anxiogenic properties with antidepressant effects. In this article, we show that antidepressant effects are partially mediated by $CRF_1$ of the dorsal hippocampus. Possible pathways responsible for the paradoxical antidepressant effects observed after $CRF_1$ activation are discussed.


*Keywords:* Corticotropin-releasing factor receptors; Cortagine; Anxiety; Depression; Elevated plus maze; Forced swim test

**Contents**



## 1. The CRF system: An overview

It has been demonstrated that many of the changes induced by stress are mediated by corticotropin-releasing factor (CRF). This 41 amino acid neuropeptide (Spiess et al., 1981) was originally characterized on the basis of its hypophysiotropic properties. It was recognized as an early chemical signal which is released from the paraventricular

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nucleus (PVN) of the hypothalamus, reaches the anterior pituitary via a portal vessel system, and stimulates the secretion of hypophyseal corticotropin (ACTH) (Vale et al., 1981). ACTH released into the general circulation subsequently stimulates the secretion of corticosterone (in rodents) from the adrenal cortex. Thus, a hormonal amplification chain is activated in response to stress. This chain represents the hypothalamic pituitary adrenal (HPA) axis generally accepted as a typical indicator of the stress response (Chadwick et al., 1993).

CRF acts through G protein-dependent receptors. Two receptor subtypes, $CRF_1$ and $CRF_2$, derived from different genes, and several splice variants have been characterized (for review, see Eckart et al., 2002). In addition to the different CRF receptor subtypes, a CRF binding protein (CRFBP) exists in the brain of rodents and humans. On the basis of the observation that approximately 50% of the total human brain CRF is bound to CRFBP (Behan et al., 1995) and, therefore, not available for CRF receptors, CRFBP represents a pharmacologically significant pool of endogenous ligand. The family of mammalian CRF-like peptides comprises four naturally occurring ligands with different CRF receptor subtype selectivities. Whereas mammalian CRF such as human/rat CRF (h/rCRF) exhibits a binding preference for $CRF_1$, the related peptide urocortin I (UcnI) (Vaughan et al., 1995) binds with high affinity to both CRF receptor subtypes. More recently, urocortin II (UcnII, also known as stresscopin-related peptide) and urocortin III (UcnIII, also known as stresscopin) have been characterized as $CRF_2$-selective agonists (Reyes et al., 2001; Hsu and Hsueh, 2001; Lewis et al., 2001; Jahn et al., 2004).

Soon after the structural analysis of ovine CRF (oCRF) purified from sheep hypothalamus, it was discovered that CRF is abundant in many regions of the brain (Swanson et al., 1983; Sawchenko and Swanson, 1985). Furthermore, the CRF receptor subtypes are distinctly distributed in the brain and the remainder of the body (Potter et al., 1994; Chalmers et al., 1995; Lovenberg et al., 1995; Van Pett et al., 2000). On the basis of pharmacological experiments and studies using transgenic mice, evidence was provided that CRF and CRF-like peptides modulate several brain functions such as anxiety, learning and memory consolidation, locomotor activity, and food intake. All these modulations may take place in the framework of the stress response, but may also be important independently of stress (Dunn and Berridge, 1990).

## 2. CRF and anxiety

### 2.1. The role of $CRF_1$

On the basis of many experiments in several laboratories, the following concept of the differential involvement of CRF receptor subtypes in anxiety has emerged. Injection of h/rCRF or oCRF, preferentially binding to $CRF_1$, into the brain ventricles generates increased anxiety-like behavior in several mouse models of anxiety (for review, see Eckart et al., 2002). Furthermore, male and female mice lacking $CRF_1$ are less anxious than mice producing this receptor subtype. The disturbance of the HPA axis indicated by low basal and stress-induced corticosterone levels (Smith et al., 1998; Timpl et al., 1998) is observed in agreement with the finding that the hypophysiotropic actions of CRF are mediated by $CRF_1$. More importantly, corticosterone replacement does not affect the anxiety profile of the mutant mice. This result supports the hypothesis that central CRF pathways modulate anxiogenic-like effects of aversive events, independent of the HPA axis (Smith et al., 1998). Consistently, conditional knockout mice in which the $CRF_1$ function is inactivated postnatally in the anterior forebrain and limbic brain structures, but not in the pituitary, show reduced anxiety, while retaining a normal activity of their HPA axis (Muller et al., 2003). Increased anxiety is also found in mice centrally over-expressing CRF (Stenzel-Poore et al., 1994), as well as in CRFBP-deficient mice (Karolyi et al., 1999). Data obtained with $CRF_1$-deficient mice are consistent with antisense studies showing anxiolytic properties of $CRF_1$ knockdown in several anxiety tests. For example, inactivation of $CRF_1$ receptor with an antisense oligonucleotide reduces the anxiogenic-like effect of CRF (Skutella et al., 1998), and produces significant anxiolytic-like effects in the defensive withdrawal paradigm (Heinrichs et al., 1997). Further details of the involvement of $CRF_1$ in anxiety-like behavior were obtained from pharmacological experiments using various synthetic non-peptidic $CRF_1$-selective antagonists (Kehne and De Lombaert, 2002). For example, CP-154,526 (Schulz et al., 1996) acts anxiolytically in a defensive withdrawal paradigm (Arborelius et al., 2000), and in attenuating stress-induced relapse to drug addiction in cocaine- and heroin-trained rats (Shaham et al., 1998). Antalarmin, an analog of CP-154,526, reduces the behavioral, neuroendocrine, and autonomic responses to stress in adult non-human primates (Habib et al., 2000). CRA1000 and CRA1001, two other low-molecular $CRF_1$ antagonists, are able to reverse the swim stress-induced reduction of the time spent in the light area in the light/dark test, although they are ineffective in non-stressed animals in the same paradigm (Okuyama et al., 1999). DMP695 dose-dependently increases punished responses of rats in a Vogel conflict test and enhances social interaction of rats in an unfamiliar environment (Millan et al., 2001). Acute doses of R121919 reduce measures of anxiety in a defensive withdrawal paradigm (Gutman et al., 2003). DMP904 increases the time spent in open arms of an elevated-plus maze (EPM). In addition, acutely or chronically administered DMP904, but only acutely applied triazolobenzodiazepine alprazolam, significantly reduces exit latency in the defensive withdrawal paradigm. It is suggested that tolerance may not develop to the anxiolytic-like effects of DMP904 in this model of anxiety (Lelas et al., 2004).