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Urocortins: CRF's siblings and their potential role in anxiety, depression and alcohol drinking behavior

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ABSTRACT

It is widely accepted that stress, anxiety, depression and alcohol abuse-related disorders are in large part controlled by corticotropin-releasing factor (CRF) receptors. However, evidence is accumulating that some of the actions on these receptors are mediated not by CRF, but by a family of related Urocortin (Ucn) peptides Ucn1, Ucn2 and Ucn3. The initial narrow focus on CRF as the potential main player acting on CRF receptors appears outdated. Instead it is suggested that CRF and the individual Ucns act in a complementary and brain region-specific fashion to regulate anxiety-related behaviors and alcohol consumption. This review, based on a symposium held in 2011 at the research meeting on "Alcoholism and Stress" in Volterra, Italy, highlights recent evidence for regulation of these behaviors by Ucns. In studies on stress and anxiety, the roles of Ucns, and in particular Ucn1, appear more visible in experiments analyzing adaptation to stressors rather than testing basal anxiety states. Based on these studies, we propose that the contribution of Ucn1 to regulating mood follows a U-like pattern with both high and low activity of Ucn1 contributing to high anxiety states. In studies on alcohol use disorders, the CRF system appears to regulate not only dependence-induced drinking, but also binge drinking and even basal consumption of alcohol. While dependence-induced and binge drinking rely on the actions of CRF on CRFR1 receptors, alcohol consumption in models of these behaviors is inhibited by actions of Ucns on CRFR2. In contrast, alcohol preference is positively influenced by actions of Ucn1, which is capable of acting on both CRFR1 and CRFR2. Because of complex distribution of Ucns in the nervous system, advances in this field will critically depend on development of new tools allowing site-specific analyses of the roles of Ucns and CRF.

Introduction

It is well known that the corticotropin-releasing factor (CRF, also known as the corticotropin-releasing hormone) peptide system is critical for the neuroendocrine and behavioral responses to stressful situations (such as anxiety and depression) in vertebrates (Bale & Vale, 2004; Hauger, Risbrough, Brauns, & Dautzenberg, 2006). Since stress is one of the risk factors of alcoholism, much evidence has been gained confirming the involvement of the CRF system in alcohol abuse and dependence (Heilig & Egli, 2006; Koob & Le Moal, 2001). However, the role of CRF system has been too often simplistically equaled with the role of CRF. This is not surprising, as historically CRF was the first peptide of the CRF system to be discovered (Vale, Spiess, Rivier, & Rivier, 1981).

It is now appreciated that the CRF system is more complex than previously thought and includes several additional players. Specifically, the CRF system includes, in addition to CRF, the three urocortin peptides (Ucn1, Ucn2 and Ucn3), two receptors types, CRFR1 and CRFR2 and the CRF-binding protein (Bale & Vale, 2004; Fekete & Zorrilla, 2006; Joels & Baram, 2009; Kuperman & Chen, 2008; Ryabinin et al., 2002; Steckler & Holsboer, 1999). Table 1 shows that Ucns bind and activate the CRFR2 with high affinity. CRF has a relatively lower affinity for CRFR2 than for CRFR1; Ucn1

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Table 1
Affinities of CRF-like peptides.

	CRF	Urocortin 1	Urocortin 2	Urocortin 3
CRFR1	Very high	Very high	Low	Low
CRFR2	Low	High-very high (species-dependent)	Very high	High
CRF-binding protein	Very high	Very high	Low-high (species-dependent)	Low

Affinities: Very high – inhibitory binding constants below 1 nM, High – inhibitory binding constants 1–10 nM, Low – inhibitory binding constants higher than 10 nM. The affinities are based on data in (Fekete & Zorrilla, 2006).

has equal affinities for both receptors; and Ucns 2 and 3 appear to be selective for CRFR2 (Hsu & Hsueh, 2001; Lewis et al., 2001; Reyes et al., 2001; Vaughan et al., 1995).

The CRF receptors are distributed differently throughout the brain: while CRFR1 is widely expressed, CRFR2 is expressed in a more discrete but partially overlapping manner. Selective expression of CRFR2 is observed in anxiety and depression-related brain nuclei, including the medial amygdala (MeA), bed nucleus of stria terminalis (BNST), lateral septum (LS) and the dorsal raphe nucleus (DRN) (Chalmers, Lovenberg, & De Souza, 1995; Steckler & Holsboer, 1999; Van Pett et al., 2000). CRF peptide has been found in the paraventricular nucleus of hypothalamus (PVN), neocortex, central nucleus of amygdala (CeA), BNST, hippocampus, raphe nuclei, periaqueductal gray, olfactory bulbs, several thalamic and brain stem nuclei and the cerebellum (Merchenthaler, Hynes, Vigh, Shally, & Petrusz, 1983; Morin, Ling, Liu, Kahl, & Gehlert, 1999; Steckler & Holsboer, 1999; Swanson, Sawchenko, Rivier, & Vale, 1983). Ucn1 in primarily expressed in the centrally-projecting Edinger-Westphal nucleus (EWcp) (Bittencourt et al., 1999; Kozicz, Yanaihara, & Arimura, 1998; Ryabinin, Tsivkovskaia, & Ryabinin, 2005; Vaughan et al., 1995). This brain region (also previously called non-preganglionic Edinger-Westphal nucleus and the perioculomotor urocortin-containing area) should be distinguished from the preganglionic Edinger-Westphal nucleus (EWpg), a cholinergic parasympathetic nucleus known for its oculomotor function, which does not contain Ucn1 (Cavani, Reiner, Cuthbertson, Bittencourt, & Toledo, 2003; Kozicz et al., 2011; May, Reiner, & Ryabinin, 2008; Ryabinin et al., 2005; Vasconcelos et al., 2003; Weitemier, Tsivkovskaia, & Ryabinin, 2005). Earlier literature did not distinguish between EWcp and EWpg, and most often referred to the site of Ucn1 as EW. Besides EWcp, the lateral superior olive and supraoptic nucleus express Ucn1, although at lower levels, and inconsistently between different species (Bittencourt et al., 1999; Spina et al., 2004; Weitemier et al., 2005). Ucn2 is expressed in the PVN, supraoptic nucleus, arcuate nucleus, locus coeruleus, the trigeminal, facial and hypoglossal motor nuclei and the meninges (Reyes et al., 2001; Tanaka et al., 2003). Ucn3 is expressed in medial preoptic area, perifornical area, BNST, MeA, ventral premammillary nucleus, superior olivary nucleus and parabrachial nucleus (Cavalcante, Sita, Mascaro, Bittencourt, & Elias, 2006; Deussing et al., 2010; Lewis et al., 2001; Li, Vaughan, Sawchenko, & Vale, 2002). It also needs to be kept in mind that differences in the distribution of these peptides and receptors between species and even lines of animals have been reported, further complicating the discussion of their function (Weitemier et al., 2005).

The pivotal role of CRF expressed in the PVN, acting on CRFR1 receptors in the pituitary and mediating the hypothalamic-pituitary-adrenal (HPA) axis response to stressors has been well established. Therefore, at first it appeared surprising that while both CRFR1 KOs and CRF KOs showed HPA deficits, deletion of CRFR1, but not CRF, lead to attenuation of anxiety-like behaviors (Weninger et al., 1999). This evidence suggested that other CRF receptor ligands (such as the Ucns) play important roles in the behavioral responses to stressors. Recent studies have focused on elucidating these roles using different methodologies and revealed the importance of Ucns in behaviors related to adaptation and maladaptation to stress, such as anxiety, depression and alcohol consumption. Importantly for alcohol research, these studies implicate the Ucns not only in dependence-induced drinking, but also in binge drinking of alcohol. This review focuses on the recent findings in this field.

Role of urocortins in adaptation to stress and anxiety: genetic evidence

While the role of the CRF-CRFR1 system in activating the HPA axis and regulating emotional and cognitive functions following exposure to stressors is well established (Arborelius, Owens, Plotsky, & Nemeroff, 1999; Holsboer, 1999; Nemeroff, 1992; Reul & Holsboer, 2002), the role of the Ucns-CRFR2 system is only beginning to be understood. Interpretation of pharmacological studies testing the roles of specific peptides in stress and anxiety has been difficult because of the partially overlapping patterns of distribution of CRF, Ucns and both types of receptors. In contrast, studies using genetic KOs of CRF receptors and their ligands have allowed distinction of some of these roles.

While CRFR1-KO mice clearly showed decreased measures of anxiety and stress (Smith et al., 1998; Timpl et al., 1998), CRFR2 KOs tended to show heightened anxiety (Bale et al., 2000; Coste et al., 2000; Kishimoto et al., 2000). Therefore, it was suggested that the CRF-CRFR1 system is essential for initiating stress responses whereas the Ucns-CRFR2 system is involved in terminating the stress response. While this hypothesis is not without contradictions, it has gained much support. However, the three independently generated CRFR2-KO mouse lines (Bale et al., 2000; Coste et al., 2000; Kishimoto et al., 2000) presented several inconsistencies in their endocrine and behavioral profiles, possibly due to differences in background lines. For example, Coste and colleagues reported an increased ACTH and CORT response to stress and an early termination of ACTH release in CRFR2-KO mice, but found no differences in anxiety-like behavior between CRFR2-KO and WT littermates (Coste et al., 2000). On the other hand, Bale and colleagues reported increased ACTH and CORT response to stress and an early termination of ACTH release in their CRFR2-KO mouse line (Bale et al., 2000). Yet, these CRFR2-KO mice exhibited a significant increase in anxiety-like behavior in the elevated plus maze (EPM) and the open field (OF), but not in the dark–light transfer (DLT), tests. In partial agreement with these phenotypes, Kishimoto and colleagues reported that CRFR2-KO male mice appear more anxious in the EPM and DLT tests, although in the OF test they spent more time in the center area, indicative of anxiolysis (Kishimoto et al., 2000). Interestingly, the latter two lines also exhibited a depression-like phenotype in the forced swim (FS) and tail suspension (TS) tests (Bale & Vale, 2003; Todorovic et al., 2009). In addition, CRFR2-KO females have been shown to have impaired maternal defense behavior of their offspring (Gammie, Hasen, Stevenson, Bale, & D'Anna, 2005) and enhanced social discrimination memory (Deussing et al., 2010).

The first two independently generated mouse Ucn1-KO models were reported to exhibit normal endocrine stress responses (Vetter et al., 2002; Wang et al., 2002), supporting the view that Ucn1 has a minor role in stress-induced HPA axis regulation. Like CRFR2-KO mice, their behavioral phenotypes were inconsistent. Whereas Wang and colleagues (Wang et al., 2002) reported no differences in anxiety-like behaviors, Vetter and colleagues (Vetter et al., 2002) reported increased anxiety-like behaviors in the EPM and OF, but