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Review

# Urocortin – From Parkinson's disease to the skeleton

K.M. Lawrence[a,b,*], T.R. Jackson[a,b], D. Jamieson[c,d], A. Stevens[e], G. Owens[a,b], B.S. Sayan[a,b], I.C. Locke[f], P.A. Townsend[a,b]

[a] Faculty Institute for Cancer Sciences, University of Manchester, Manchester Academic Health Science Centre, St Mary's Hospital, Research Floor, Oxford Road, Manchester M13 9WL, UK
[b] Manchester Centre for Cellular Metabolism, FMHS, UoM, M13 9WL, UK
[c] Faculty of Life Sciences, Michael Smith Building, University of Manchester, M13 9WL, UK
[d] Biorelate Ltd, Manchester, UK
[e] Faculty of Medical and Human Sciences, University of Manchester and Royal Manchester Children's Hospital, Manchester M13 9WL, UK
[f] Department of Biomedical Sciences, University of Westminster, 115 New Cavendish Street, London W1W 6UW, UK

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ABSTRACT

Urocortin (Ucn 1), a 40 amino acid long peptide related to corticotropin releasing factor (CRF) was discovered 19 years ago, based on its sequence homology to the parent molecule. Its existence was inferred in the CNS because of anatomical and pharmacological discrepancies between CRF and its two receptor subtypes. Although originally found in the brain, where it has opposing actions to CRF and therefore confers stress-coping mechanisms, Ucn 1 has subsequently been found throughout the periphery including heart, lung, skin, and immune cells. It is now well established that this small peptide is involved in a multitude of physiological and pathophysiological processes, due to its receptor subtype distribution and promiscuity in second messenger signalling pathways. As a result of extensive studies in this field, there are now well over one thousand peer reviewed publications involving Ucn 1. In this review, we intend to highlight some of the less well known actions of Ucn 1 and in particular its role in neuronal cell protection and maintenance of the skeletal system, both by conventional methods of reviewing the literature and using bioinformatics, to highlight further associations between Ucn 1 and disease conditions. Understanding how Ucn 1 works in these tissues, will help to unravel its role in normal and pathophysiological processes. This would ultimately allow the generation of putative medical interventions for the alleviation of important diseases such as Parkinson's disease, arthritis, and osteoporosis.


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*Abbreviations:* Ucn 1, urocortin; CRF, corticotropin releasing hormone; CRF-R, corticotropin releasing hormone receptor; PD, Parkinson's disease; SN, substantia nigra; GSK-3β, glycogen synthase kinase- 3β; HDAC, histone deacetylase; RA, rheumatoid arthritis; OA, osteoarthritis; OP, osteoporosis; Ch, chondrocyte; Oc, osteoclast; Ob, osteoblast.

* Corresponding author. Tel.: +44 01617017559x17559; fax: +44 01617016919.
*E-mail address:* kevin.lawrence@manchester.ac.uk (K.M. Lawrence).

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## 1. Introduction

Peptides originally discovered in the brain and subsequently demonstrated to have a physiological role there, were often classified under the umbrella of "neuropeptide", implying that these molecules were specific to the brain. Although many have origins in the brain, they can also be released, or induce the release of related factors into the circulation, where they can exert their effects on diverse peripheral tissues. Recently, many of these molecules have been found to also exist in peripheral tissues, making the term neuropeptide redundant (Iversen et al., 1978). First cloned in 1981 by Spiess et al. (1981), CRF is an example of such a peptide. This 41 amino acid peptide was originally described as a hypothalamic hormone, responsible for the release of ACTH from the anterior pituitary gland, which then enters the circulation and ultimately causes the release of cortisol from the adrenal cortex (Smith and Vale, 2006). The original proposed role of CRF was as a key activator of the hypothalamus-pituitary-adrenal (HPA) axis and as such has a crucial role in the stress response.

It had long been known that CRF binds to two different G-protein coupled receptors, CRF receptor 1 (CRF-R1) and 2 (CRF-R2), both the product of independent genes and subject to extensive alternative RNA splicing (Hauger et al., 2003; Perrin and Vale, 1999). However, investigators soon identified certain anatomical and pharmacological anomalies with this relationship. Firstly, there was a very poor correlation between the sites of expression of CRF-R2 in the brain and CRF itself and secondly, CRF had a relatively low binding affinity for CRF-R2. Both pieces of evidence suggested the existence of at least one more related ligand and in 1995 Vaughan and colleagues used homology cloning based on the sequence of CRF to identify a second member of this family, the 40 amino acid peptide, Ucn 1 (Vaughan et al., 1995). Since then, two further paralogues of Ucn 1 have been isolated; Ucn 2 (Human Stresscopin Related Peptide), and Ucn 3 (Human Stresscopin), which are composed of 38 and 39 amino acids respectively (Hsu and Hsueh, 2001). Radioligand binding studies have revealed that CRF and Ucn 1 have affinity for both receptor subtypes, but Ucn 1 is significantly more potent than CRF on CRF-R2, whereas Ucn 2 and 3 bind exclusively to CRF-R2 (Perrin and Vale, 1999). These peptides are evolutionary ancient molecules having representatives in lower vertebrates such as sauvagine in amphibia and urotensin in fish (Lovejoy, 2009; Lovejoy and Balment, 1999). In fact, the name urocortin is an amalgam of fish urotensin and corticotropin. This system is completed by corticortropin releasing factor-binding protein (CRF-BP), which acts as a pseudo-receptor for both CRF and Ucn 1 (Behan et al., 1996; Seasholtz et al., 2002), suggesting that this family of receptors and ligands may be self-regulating.

These peptides and proteins were originally found in the brain and played an important role in the regulation of the HPA axis and the stress response, however, their specific functions in the stress response differ. CRF actions are stressful, whereas those of Ucn 1 are stress-coping (Reul and Holsboer, 2002). The CRF family peptides are now known to be localised to every major organ of the body where they exert local actions on tissues and cells in both an autocrine and paracrine manner. These peptides are highly pleiotropic, having wonderfully diverse modes of action resulting from a combination of factors depending on the tissue type. Firstly, the peptides display markedly different affinities for the two classes of CRF receptors. Secondly, they also exhibit a remarkable degree of receptor signalling promiscuity (Brar et al., 2002; Grammatopoulos et al., 2000; Graziani et al., 2002; Lawrence and Latchman, 2006) (Fig. 1). This is facilitated by their ability to couple to multiple G-proteins, even within the same cell. The consequence of this is the regulation of diverse intracellular networks that involve numerous effectors such as cAMP, intracellular ions, and an array of protein kinases, ultimately resulting in altered gene expression (Barry et al., 2010; Lawrence et al., 2002). Common signalling pathways utilised by these peptides include mitogen-activated protein kinase (MAPK) pathways, in particular the extracellular signal-regulated kinases (ERKs). ERK1/2 constitute a widely conserved family of serine threonine protein kinases involved in many cellular functions such as cell proliferation, cell differentiation, cell movement, and cell survival (MacCorkle and Tan, 2005).

As a result of their multiple cellular activities, it is becoming apparent that these peptides are involved in numerous normal and pathological states and that by understanding their modes of action in various tissues, it may be possible to manipulate this system for clinical gain and to develop novel treatments for numerous CNS and peripheral disorders. Many of the well-known actions of Ucn 1 such as its role in mood disorders, or its effects on peripheral systems such as the cardiovascular and immune systems, have been extensively reviewed elsewhere (Baigent, 2001; Davidson and Yellon, 2009; Fekete and Zorrilla, 2007; Gravanis and Margioris, 2005; Yang et al., 2008). The aim of this review therefore, is to focus on some of the lesser known effects of Ucn 1, such as its role in neurodegeneration in Parkinson's disease and disorders of the skeletal system. These examples are selected with the intention of highlighting how the understanding of Ucn 1's mechanisms of action is expanding further, along with the diverse therapeutic potential of Ucn1 itself, Ucn 1 mimetics, or Ucn 1 receptor antagonists.

## 2. Urocortin and Parkinson's disease

Although the exact cause of Parkinson's disease (PD) is unknown, the most consistent anatomical feature is severe degeneration of the dopaminergic neurones of the Substantia Nigra (SN) and striatum (Foltynie and Kahan, 2013; Samii et al., 2004), which in humans, results in characteristic motor abnormalities such as tremor, rigidity, hypokinesia, and postural instability (Meissner, 2012). Histologically, these neurones exhibit a characteristic cocktail of toxic cellular inclusions; Lewy bodies, neurofibrillary tangles, and an enrichment of α-synuclein (Breydo et al., 2012; Forno, 1996; Lei et al., 2010). It has been estimated that up to 80% of neuronal death occurs in the dopaminergic SN pars compacta before clinical manifestations of PD appear. Although the precise cause of the inevitable neuronal demise remains nebulous, potential contributing factors include glutamatergic excitotoxicity (Duty, 2010), elevated free-radical production (Surendran and Rajasankar, 2010), neuroinflammatory events (Tufekci et al., 2012), and overexpression of Parkinsonian genes, in particular the ubiquitin ligase Parkin (Springer and Kahle, 2011). Whatever the cause of this neuronal cell death, it is thought to be mainly apoptotic in nature (da Costa and Checler, 2011; Perier et al., 2012; Venderova and Park, 2012). Clearly, a compound which possesses the ability to prevent cellular apoptosis, free radical damage, and inflammation would be a good candidate as a protective agent against the ravages of PD. These three prerequisites have been found for Ucn 1 in other tissues (Lawrence and Latchman, 2006; Barry et al., 2010; Baigent, 2001). The abundant expression of both Ucn 1 and its cognate receptors in dopaminergic neurons and astroglia of the SN, suggests that Ucn 1 plays a role in PD pathophysiology (Yamamoto et al., 1998). However, at present, there is no data concerning altered expression levels of Ucn 1 in PD. The most convincing in vivo study implicating Ucn 1 as a neuroprotective agent in PD was conducted by Abuirmeileh (Abuirmeileh et al., 2007a,b, 2008, 2009), using the classical 6-hydroxydopamine (6-OHDA) lesion, and lipopolysaccharide (LPS) induced pro-inflammatory toxicity models to generate parkinsonism in rats. Upon stereotactic targeting to dopaminergic neurones of the SN, both insults increased the characteristic apomorphine induced circular motor activity, known to accompany neuronal ablation, with an associated loss of