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Commentary

Urocortins in heart failure

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ABSTRACT

Despite modern advances in the treatment of the causes and consequences of cardiovascular illness, heart disease and heart failure remain a leading cause of death in the western world. Many novel peptides are emerging as biomarkers and potential therapeutic tools for this debilitating condition. Urocortins represent one such group of peptides whose role in normal cardiovascular physiology and disease states is now increasingly being recognized. The cardiovascular effects of the urocortins are mediated via corticotrophin-releasing hormone (CRH) receptors through a variety of intra-cellular signaling pathways. Studies to date have demonstrated a favourable effect of urocortins on hemodynamic and neurohumoral regulation. They cause relaxation of the vasculature as well as having positive inotropic, chronotropic and lusitropic effects on the heart. This makes the urocortins a potentially attractive target in the treatment of heart failure. Indeed, a number of studies have demonstrated increased urocortin activity in experimental and clinical heart failure, with apparent augmented responses in these states. This article provides a review of the role of urocortins in normal cardiovascular physiology and in the pathophysiology of heart failure.

1. Introduction

Despite modern advances in the treatment of the causes and consequences of cardiovascular illness, heart disease remains a leading cause of death in the western world. In particular, heart failure continues to carry a poor prognosis with a considerable burden on the health care system throughout the world: the estimated direct cost for heart failure in the United States was $30 billion in 2006 [1]. Many novel peptides are emerging as biomarkers and potential therapeutic tools for this debilitating condition. Urocortins represent one such group of peptides whose role in normal cardiovascular physiology and disease states is now being increasingly recognized. After their initial discovery in 1995 [2], subsequent research has furthered understanding of their mechanisms, predominantly in pre-clinical models, with expansion of this knowledge into potential therapeutic applications in humans. This article provides a review of the role of urocortins in normal cardiovascular physiology and in the pathophysiology of heart failure.

2. The urocortin–CRH system

Urocortins belong to the corticotrophin-releasing hormone (CRH) family which includes CRH, fish urotensin I, frog sauvagine, urocortin 1, urocortin 2 and urocortin 3 [3] (Fig. 1). CRH is produced in the brain in response to stress, has central effects upon behaviour, and exerts a variety of peripheral responses. However, CRH is unlikely to have major effects upon cardiac function as it is not expressed locally and its plasma concentrations are very low.

In 1995, Vaughan et al. [4] observed urotensin-like immunoreactivity in the Edinger Westphal nucleus and lateral superior olive regions of the adult rat brain. It was named urocortin (now known as urocortin 1) to reflect its similarities of structure and biological properties to urotensin (suckerfish urotensin) and rat CRH. It is believed to be the second endogenous mammalian ligand for CRH receptors [5]. Subsequently, two further paralogues of CRH were identified—urocortin 2 and urocortin 3. Human CRH and urocortin 1 genes have been localized to chromosomes 8 (8q13) and 2 (2p23-p21), respectively. Urocortin 2 and urocortin 3 have prominent cardiovascular roles and are expressed in the heart. In contrast to CRH, the urocortins do not increase corticosterone secretion and do not appear to have any physiologic role in the regulation of the hypothalamic–pituitary–adrenal axis [6,7].

2.1. CRH receptors

The effect of CRH and urocortins is mediated via CRH receptors (CRH-R). These seven transmembrane G-protein coupled receptors are members of the secretin family [8] and the human CRH-R gene has been localized to chromosomes 17 (17q12-qter) and 7 (7p21-p15) [9,10]. Two subtypes of CRH receptors have been identified in mammals and rodents—CRF-R1 and -R2. Structurally, the two

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	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
CRH	S	E	E	P	P	I	S	L	D	L	T	F	H	L	L	R	E	V	L	E	M
Urocortin		D	D	P	P	L	S	I	D	L	T	F	H	L	L	R	T	L	L	E	L
Urocortin 2				V	I	L	S	L	D	V	P	I	G	L	L	R	I	L	L	E	Q
Urocortin 3				F	T	L	S	L	D	V	P	T	N	I	M	N	I	L	F	N	I
Sauvagine		E	G	P	P	I	S	L	D	L	S	L	E	L	L	R	K	M	I	E	I
Urotensin 1	N	D	D	P	P	I	S	L	D	L	T	F	H	L	L	R	N	M	I	E	M

	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41
CRH	A	R	A	E	Q	L	A	Q	Q	A	H	S	N	R	K	L	M	E	I	I
Urocortin	A	R	T	Q	S	Q	R	E	R	A	E	Q	N	R	I	I	F	D	S	V
Urocortin 2	A	R	Y	K	A	A	R	N	Q	A	A	T	N	A	Q	I	L	A	H	V
Urocortin 3	D	K	A	K	N	L	R	A	K	A	A	A	N	A	Q	L	M	A	Q	I
Sauvagine	E	K	Q	E	K	E	K	Q	Q	A	A	N	N	R	L	L	L	D	T	I
Urotensin 1	A	R	I	E	N	E	R	E	Q	A	G	L	N	R	K	Y	L	D	E	V

Fig. 1. Amino acid sequences of CRH and its analogue peptides. Sequences shown are that of mammalian CRH and urocortins, amphibian sauvagine and teleost urotensin 1. Highlighted sequences represent similarity to CRH.

subtypes exhibit considerable divergence at the N terminus, consistent with their distinct pharmacological properties. Furthermore, three splice variants of CRH-R2 have been identified. These variants differ in the structure of their N-terminal extra-cellular domain. R2α and R2β have been observed in rodents and in man, whilst R2γ is specific to humans (isolated in the limbic regions of the human brain) [8]. It is, however, unclear whether the γ splice variant has any specific physiological role. Low homology of the extra-cellular domains of CRH-R1 and -R2 accounts for differences in their ligand specificity [8]. Urocortin 1 and CRH both act at CRH-R1 but the affinity of urocortin 1 for CRH-R2 is more than 10-fold higher than that of CRH [5]. Whilst urocortin 1 can activate both receptors, urocortins 2 and 3 are potent and specific agonists at CRH-R2 [4,11] with little effect at CRH-R1.

3. Biology of urocortins

3.1. Anatomy (tissue distribution of urocortins and CRH receptors)

Immunoreactivity to the urocortins and their receptors has been demonstrated in the central nervous, digestive, reproductive, cardiovascular, immune and endocrine systems, suggesting important roles throughout the body [12]. In the brain, urocortin 1 is most prominent in the Edinger Westphal nucleus and lateral superior olive. Urocortin 1 mRNA or immunoreactivity has also been reported in other regions of the brain, such as the cerebellum and hypothalamus [8], and it appears to be co-localized with dopamine in the basal ganglia and hypothalamus. Urocortin 1 mRNA is also expressed in vascular smooth muscle cells and in cardiac myocytes. Urocortin 2 has a similar distribution in the central nervous system in mouse and rats, but is also seen in high concentrations in the peripheral tissues including the heart, adrenals, placenta, stomach, ovary, skin, gastrointestinal tract, uterine smooth muscle, skeletal muscle and peripheral blood vessels [8].

The distribution of urocortin 3 is distinct. In the central nervous system, it is demonstrable in regions of high CRH-R2 expression, supporting the notion that it is an endogenous ligand [8]. In humans, urocortin 3 is also seen in peripheral tissues such as adrenals, heart and kidney—particularly in the distal tubules [13].

CRH-R1 is predominantly found in the central nervous system. In addition to its central nervous system expression, CRH-R2 is found in peripheral tissues such as the gut, heart, lymphocytes and adrenals. In humans, urocortin 1 and CRH-R2α has been identified in all four chambers of the heart, suggesting that urocortin acts in an autocrine or paracrine fashion through CRH-Rs [14]. In contrast to rats where CRH-R2β is the predominant splice variant in the heart and vascular smooth muscle cells, humans appear to predominantly express CRH-R2α in these tissues. CRH-R2 has also been characterized in the human left ventricle and intramyocardial blood vessels [15]. In humans, both CRH-R1 and -R2 are found in the periphery, although their specific role remains to be fully characterized in human physiology and pathophysiology.

3.2. Biochemistry

3.2.1. Molecular structure

Urocortin is a 40 amino acid-containing neuropeptide, related to urotensin (63% sequence identity) and CRH (45% sequence identity) [4]. Rat and human urocortin bear 95% homology to each other. The precursor protein contains 122 amino acid residues with an N-terminal methionine and consensus signal peptide sequence, whilst the carboxy terminus of the precursor contains the C terminally amidated peptide of urocortin. The CRH analogue peptides possess an α helical conformation with varying degrees of amphipathicity. The amphipathic N-terminal helices could play a crucial role in selectivity of the analogues to CRH-R1, whereas it may not be as important for CRH-R2 binding [16]. The parent protein is half the length of urotensin and CRH precursors with little sequence similarity to either [8]. Urocortin 2 shows moderate homology with human and rat CRH (34%), urocortin 1 (43%) and urocortin 3 (37–40%). The half-life of urocortin 1 in healthy humans and those with stable heart failure is approximately 50 min [17,18]. Urocortin 2 has a shorter half-life of 10 min in