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The apelin–APJ system in heart failure Pathophysiologic relevance and therapeutic potential

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ABSTRACT

Apelin is the endogenous ligand for the previously orphaned G protein-coupled receptor, APJ. This novel peptidic signalling pathway is widely represented in the heart and vasculature, and is emerging as an important regulator of cardiovascular homeostasis. In preclinical models, apelin causes nitric oxide-dependent vasodilatation, reduces ventricular preload and afterload, and increases cardiac contractility in rats with normal and failing hearts. Apelin–APJ signalling also attenuates ischemic myocardial injury and maintains cardiac performance in ageing and chronic pressure overload. Downregulation of apelin and APJ expression coincides with declining cardiac performance raising the possibility that diminished apelin–APJ activity may have pathophysiologic implications. At present, data from human studies is limited but changes in apelin and APJ expression in patients with chronic heart failure parallel those seen in preclinical models. Detailed clinical investigation is now required to establish the role of apelin in human cardiovascular physiology and pathophysiology, and to determine the therapeutic potential of augmenting apelin signalling in patients with heart failure.

1. Introduction

Heart failure constitutes a major and growing health burden in developed nations. Despite considerable treatment advances over the past two decades, it has a prognosis worse than that of many cancers and results in severe morbidity with impaired quality of life and recurrent hospitalisation [1,2]. The development of novel treatments for patients with heart failure therefore remains a major priority. G protein-coupled receptors (GPCRs) play an essential role in the physiological control of the cardiovascular system and represent a major target for existing pharmacological treatments [3,4]. Many of the recent pharmacological advances in the treatment of heart failure, including angiotensin II type 1 (AT1) and beta-adrenergic receptor blockers, have arisen through the specific targeting of GPCR systems, and have provided additive incremental morbidity and mortality benefits [5,6].

In 1993 a novel GPCR called APJ was identified through the Human Genome Project [7]. Despite sharing significant sequence homology with AT1, APJ did not display specific binding for angiotensin II and remained orphaned until 1998 when its endogenous ligand was identified from bovine stomach extracts and named apelin (APJ endogenous ligand) [8]. Since its discovery, the apelin–APJ system has emerged as an important regulator of cardiovascular homeostasis that may play a role in the pathophysiology of heart failure and represents an exciting target for the development of new therapies [9–11].

In this article we will review the biology of the apelin–APJ system and its role in cardiovascular homeostasis. We will then discuss the evidence for altered apelin–APJ regulation in the setting of heart failure and consider how attenuated apelin signalling may contribute to the pathophysiology of this condition. Finally we will explore the therapeutic potential of

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targeting the apelin–APJ system in heart failure and, in particular, the rationale for augmenting apelin–APJ activity as a means of preserving and restoring cardiac performance.

2. The apelin–APJ system

2.1. Apelin

The apelin gene, located on the long arm of the human X chromosome, encodes a 77 amino acid preproprotein that is then cleaved to shorter active peptides (Fig. 1) [8,12,13]. The full-length mature peptide comprises 36 amino acids (apelin-36) and was originally isolated from bovine stomach extracts. Gel filtration chromatography of bovine colostrum confirmed the presence of apelin-36 and revealed a second peak of activity corresponding to a 13 amino acid peptide (apelin-13), which has subsequently been identified in several other tissues. The 13 amino acid peptide possesses a pyroglutamate substitution at the N-terminus; a common post-translational modification that preserves biological activity by rendering the peptide more resistant to enzymatic cleavage. Although not yet identified *in vivo*, the existence of other endogenous apelin isoforms is predicted by several potential proteolytic cleavage sites on apelin-36. Accordingly, synthetic C-terminal fragments of apelin-36 including apelin-19, apelin-17, apelin-16 and apelin-12 also activate the APJ receptor [8,13–18] though fragments shorter than 12 amino acids are biologically inert. The shorter apelin isoforms exhibit greater binding affinity and biological potency than the full-length peptide, the most potent being the pyroglutamated form of apelin-13 that may represent the principally active biological ligand [13,15,16].

Expression of the apelin gene is increased in response to hypoxia under the regulation of hypoxia-inducible factor-1 [19]. In breast tissue there is up-regulation of apelin synthesis during lactation that is mediated by upstream stimulatory factor-1 [20], a fairly ubiquitous transcription factor involved primarily in energy metabolism and cellular proliferation [21]. In adipocytes, apelin gene expression is inhibited in the fasting state and stimulated by refeeding possibly through changes in the plasma concentrations of insulin and counter-regulatory hormones [22,23]. Finally, in magnocellular neurons of the hypothalamus, apelin is upregulated by dehydration, through a mechanism that may involve arginine vasopressin [24].

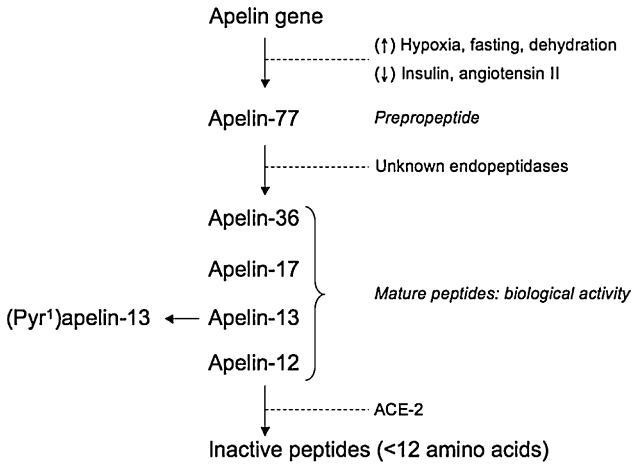

Fig. 1 – Apelin synthesis, post-translational processing and metabolism.

Less is known about the mechanisms regulating the post-translational processing of apelin including the proteolytic cleavage of the longer apelin isoforms to shorter C-terminal fragments and the pyroglutamine modification of the apelin-13. One enzyme implicated in the processing of apelin peptides is angiotensin-converting enzyme (ACE) type 2 [25], a carboxypeptidase that negatively regulates the renin–angiotensin–aldosterone system (RAAS) by cleaving angiotensin II to the biologically inactive peptide angiotensin 1–9 or angiotensin 1–7 [26]. ACE-2 has been reported to hydrolyse both apelin-13 and apelin-36 with high catalytic efficiency [25]. To our knowledge this is the only degradation pathway for apelin yet described, although its physiological significance remains unclear [11].

2.2. The APJ receptor

The human APJ gene is located on the long arm of chromosome 11 and encodes a 377 amino acid G protein-coupled receptor with seven transmembrane-spanning domains [7] for which apelin is the only known ligand. The transcriptional regulation of the APJ gene appears to be complex and, at the time of writing, remains poorly understood. Physiological stimuli for APJ synthesis include acute and chronic stress, salt loading and water deprivation. At the molecular level, a TATA-less promoter region within the gene has recently been identified [27]. The transcriptional factor, Sp1, which initiates transcription of several genes whose promoters lack a TATA box [28], also plays a major role in activation of the APJ promoter. Other factors that contribute to promoter activity include CCAAT/enhancer binding protein, estrogen and glucocorticoid protein complexes [27].

3. Biology of the apelin–APJ system

3.1. Anatomy: tissue localisation of APJ and apelin

The apelin–APJ system has wide representation in the central nervous system and a variety of peripheral tissues (Fig. 2; for review see ref. [9]). In some tissues, such as lung, kidney and adrenal gland, APJ expression may be restricted to the vasculature, though out with the cardiovascular system, APJ receptors have been detected in neurons of the cerebral cortex, hippocampus and hypothalamus, pituitary gland cells, enterochromaffin-like gastric cells, pancreatic islet cells, osteoblasts and T-lymphocytes. The expression pattern of apelin is closely related to that of APJ with co-localisation of the receptor and ligand in many tissues, suggesting a possible autocrine or paracrine signalling pathway. However, apelin is also expressed in cell types lacking the APJ receptor such as adipocytes and has been detected in plasma at levels consistent with a circulating hormone.

Within the human vasculature, both APJ receptor-like immunoreactivity (APJ-LI) and apelin-like immunoreactivity (apelin-LI) are detectable in endothelial cells and vascular smooth muscle cells of human large conduit vessels including