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Original Article

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Apelin: A promising therapeutic target?

(Part 1)

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Abstract

Apelin is a recently discovered bioactive peptide, known to be an endogenous high-affinity ligand for the previously orphan G protein-coupled receptor APJ. Apelin/APJ as a novel signaling pathway has been shown to play many crucial roles in cardiovascular function, blood pressure regulation, fluid homeostasis, feeding behavior, obesity, type 2 diabetes mellitus, adipoinsular axis regulation, cell proliferation, angiogenesis, neuroprotection and thermoregulation. This ubiquitous peptide opens a new field of research in biology and medicine. In this regard, the aim of this short review is to compile the evidence for the apelin involvement in modulation of cardiovascular system and introduction of this new peptidic pathway as a useful drug target in the treatment of cardiovascular diseases in future.

Keywords: Apelin, APJ, G-protein coupled receptor, Heart failure, Nitric oxide, Hypertension, Atherosclerosis

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Introduction

Angiotensin receptor-like 1 (APJ) is a member of G protein-coupled receptors, identified in 1993 (O'Dowd et al., 1993). APJ remained an orphan receptor until its endogenous multifunctional ligand apelin (APJ endogenous ligand) was purified from bovine stomach extracts in 1998 (Tatemoto et al., 1998). Apelin/APJ system is a novel signaling pathway with different physiological functions. This signaling system also provide a potential drug target for developing new therapies.

Synthesis

Apelin

The apelin gene is located on X chromosome at Xq25-q26.3, encoding a 77 amino acid prepropeptide, followed by an enzymatic cleavage (unknown endopeptidases). The peptide is broken to fragments of different sizes e.g. apelin-36, apelin-17, apelin-13 and apelin-12. The shorter isoforms possess greater binding affinity and biological potency (Habata et al., 1999; Hosoya et al., 2000; Kawamata et al., 2001). The only apelin degradation pathway identified to date is angiotensin-converting enzyme type 2 pathway (Japp & Newby 2008; Masri et al., 2005).

APJ receptor

The APJ gene is mapped to chromosome 11 at 11q12, encoding a 377 amino acid G protein-coupled receptor, with seven transmembrane domains. Apelin is the only identified ligand of this receptor. Despite sharing a considerable sequence similarity with AT1 (angiotensin II type 1), this novel receptor did not display a significant binding affinity to angiotensin II, thereby has remained as an orphan receptor until 1998, when apelin was identified (Calebiro et al., 2010; Castan-Laurell et al., 2011; O'Dowd et al., 1993; Tatemoto et al., 1998). APJ couples through Gi/o and probably Gq (Kleinz & Davenport, 2005; Wettschureck & Offermanns, 2005).

Apelin/APJ tissue localization

Apelin/APJ system is widely represented in both central nervous system (e.g. cerebral cortex, hypothalamus, hippocampus and pituitary gland) and peripheral tissues including heart, liver, kidney, testis, ovary, mammary glands, lung, gastric mucosa, human vasculature (endothelial cells and vascular smooth muscle cells of large conduit vessels, small arteries and veins), pancreatic islet cells, osteoblasts, T-lymphocytes and adipose tissue. Apelin is present in the endoplasmic reticulum, Golgi apparatus and secretory vesicles (intracellular localization), (Falcão-Pires & Leite-Moreira, 2005; Kleinz & Davenport, 2005; Kleinz & Davenport, 2004).

Apelin system as a possible drug target

Cardiovascular system

Vascular effects

Apelin and APJ are expressed in the vessels (Carpéné et al., 2007). The first evidence for this notion is a rapid and transient reduction in mean arterial pressure after apelin injection in rats. While this result was observed in many other studies on rodents, in an ovine model, a biphasic haemodynamic response was observed at equivalent doses used in rodents (Charles CJ et al., 2006; El Messari et al., 2004; Lee et al., 2000). The hypotensive effect was abolished by co-administration of a non-selective NOS (nitric oxide synthase) inhibitor L-NAME (L-NG-Nitroarginine methyl ester) which suggests a nitric oxide (NO)-mediated arterial vasodilatation (Tatemoto et al., 2001). Apelin also promotes activation of endothelial NOS (eNOS) and increases the release of NO which results in an increased level of cGMP (cyclic guanosin monophosphate), ultimately resulting in relaxation of vascular musculature (Falcão-Pires & Leite-Moreira, 2005;

Ishida et al., 2004). Apelin directly activates L-arginine/NOS/NO pathway in vascular system, which may be an important mechanism in regulation of vascular function (Jia et al., 2007). Apelin can function as an arterial and venous dilator. Some studies have shown that apelin is a more effective venodilator than either hydralazine or nitrates are (Ashley et al., 2005; Japp & Newby, 2008). Apelin vascular functions extend beyond activation of eNOS. Data indicate that apelin peptides may act directly on vascular smooth muscle APJ receptors and induce vasoconstriction. However, in the presence of a functioning endothelium NO production through endothelial APJ receptor outweighs this effect. This notion implies that apelin functions as both an endothelium-dependent vasodilator and an endothelium-independent vasoconstrictor (Japp & Newby, 2008; Maguire et al., 2009), (Fig. 1).

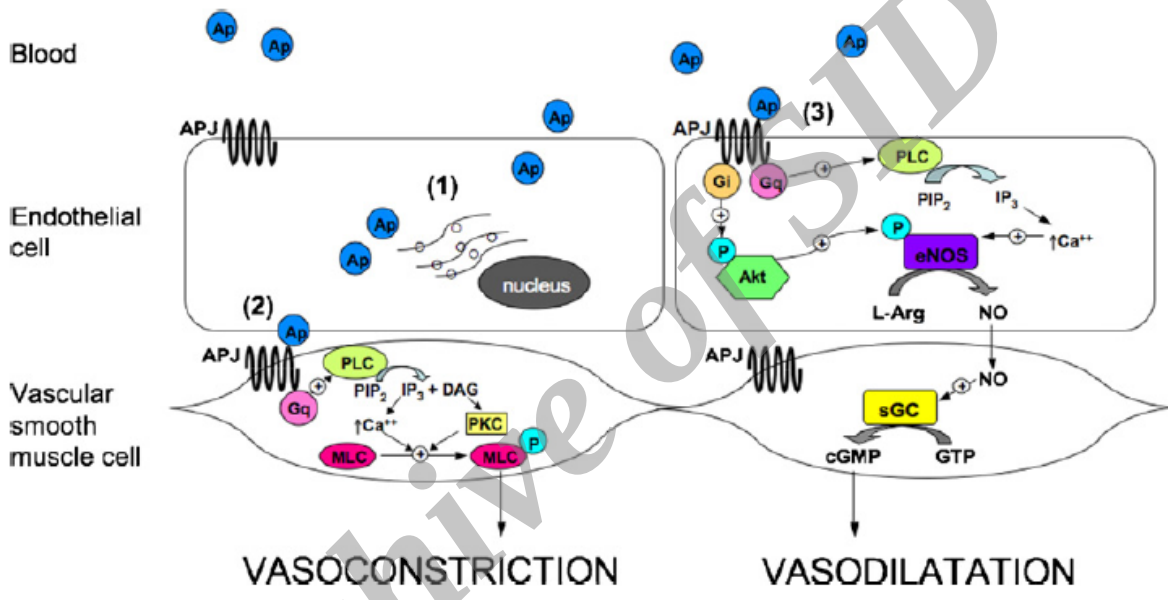

Figure 1: Hypothesised mechanisms of apelin in vascular tone regulation.
[1] Apelin peptide is synthesised in endothelial cells then transported to luminal and basolateral cell membranes. [2] Apelin directly activates APJ receptors on vascular smooth muscle cells leading to vasoconstriction. [3] Apelin activates endothelial APJ receptors and results in NO release; NO then diffuses into smooth muscle cells and results in vasodilatation. In the presence of intact endothelium the net effect is vasodilatation. Ap, apelin; P, phosphate; Gi, inhibitory G protein; Gq, Gq protein; PLC, phospholipase C; PKC, protein kinase C; IP3, inositol-3,4,5-trisphosphate; DAG, diacylglycerol; NO, nitric oxide; sGC, soluble guanylate cyclase; eNOS, endothelial nitric oxide synthase; PIP2, phosphatidylinositol bisphosphate; MLC, myosin light chain; L-Arg, L-Arginine; cGMP, cyclic guanosine monophosphate; GTP, guanosine triphosphate (Japp & Newby, 2008).

Cardiac effects

Apelin peptide is one of the most important regulators of cardiac function, exhibiting direct myocardial effects. Apelin has been shown to have a role in cardiac contractility modulation (Maguire et al., 2009); apelin increases contractility in isolated rat hearts (Szokodi et al., 2002). The studies showed a positive inotropic effect for apelin peptide (Szokodi et al., 2002). A possible mechanism for apelin-mediated inotropy includes the involvement of sacrolemmal Na^+/H^+ exchanger, probably via a phospholipase C and protein kinase C dependent pathway, leading to an increased level of intracellular Ca^{2+} as well as sensitization of myo-

filaments to Ca^{2+} (resembles levosimendan). These events ultimately leads to an increased intracellular pH and stimulation of the reverse Na^{+}/Ca^{+} exchanger (Farkasfalvi et al., 2007; Japp & Newby, 2008; Kentish, 1999), (Fig. 2). These data indicate the potential involvement of apelin/APJ system in some cardiovascular diseases, which opens a promising avenue for discovering new therapeutic agents.

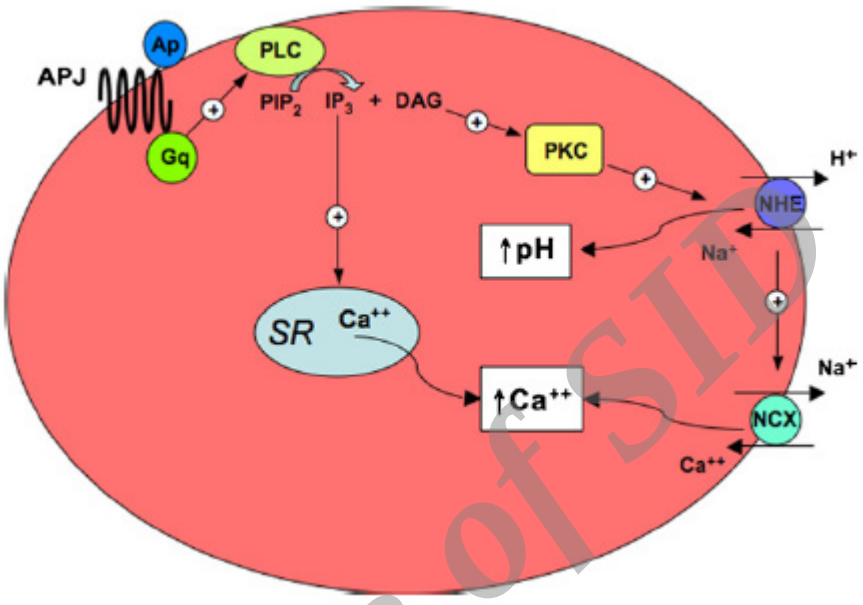

Figure 2: The possible mechanisms in apelin-mediated positive inotropy.
Ap, apelin; Gq, Gq protein; PLC, phospholipase C; SR, sacroplasmic reticulum; NHE, Na+/H+ exchanger; NCX, reverse Na+/Ca2+ exchanger; APJ, APJ receptor; PKC, protein kinase C; PIP2, phosphatidylinositol bisphosphate; IP3, inositol 1,4,5-trisphosphate; DAG, diacylglycerol (Japp & Newby, 2008).

Cardiovascular diseases and apelin/APJ axis

Apelinergic system is considered as a novel target in heart failure (HF), (Japp & Newby, 2008). Studies suggest that apelin may help prevention of left ventricular systolic dysfunction (LVSD) and the onset of HF. Secretion of this peptide will slow down the adverse left ventricular remodeling process via maintaining the cardiac output and afterload reduction. In addition, apelin may prevent excessive fluid retention due to an effect on central vasopressin release (Chandrasekaran et al., 2010). It is evident that apelin peptide improves cardiac function and lowers the blood pressure in the chronic two-kidney-one clip (2K1C) hypertension model in rats. This promises novel treatment strategies for cardiovascular complications of chronic reno-vascular conditions (Najafipour et al., 2012). Studies demonstrated that apelin level increases significantly in human atherosclerotic coronary artery and atherosclerotic plaque which may exert both beneficial and detrimental effects (Hashimoto et al., 2007; Kojima et al., 2010; Pitkin et al, 2010). On the one hand, apelin promotes smooth muscle cell proliferation and migration in to the neointima, mediates oxidative stress in vascular tissues, and when present in high levels may contribute to atherogenesis (Hashimoto et al., 2007; Li et al., 2008; Pitkin et al, 2010). On the other hand, apelin limits atherosclerotic progression by inhibiting the effects of angiotensin II on the vasculature and

also decreases macrophage infiltration (Chun et al., 2008; Leeper et al., 2009; Pitkin et al, 2010). In addition, apelin/APJ system shows protective effects in ischemic heart disease. Evidence show that apelin improves cardiac dysfunction after myocardial ischemia/reperfusion injury by suppressing the apoptosis and resisting oxidation effects. These protective effects are mediated by up-regulation of eNOS and phosphorylating Phosphatidylinositide 3-kinases (PI3K)-Akt and ERK1/2 (extracellular-signal-regulated kinases) pathways, indicating the system as an important therapy target (Simpkin et al., 2007; Zeng et al., 2009). Furthermore, apelin may be considered as a novel diagnostic plasma marker to distinguish pulmonary causes of dyspnea from its cardiovascular causes (Goetze et al., 2006).

Conclusion

In summary, apelin as a mediator peptide possessing many regulatory roles throughout the body. Apelin wide distribution suggests both autocrine and paracrine functions for this peptide. Studies have shown the potential value of this axis in the treatment of several conditions. The pathway of apelin/APJ is an interesting target in designing therapeutic agents. However, more clinical investigations are required to gain insight into the safety of apelin administration in human and clarify the contribution of this peptide to different diseases.

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