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APpEaLING therapeutic target for obesity cardiomyopathy?

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Obesity-associated co-morbidities include insulin resistance, glucose intolerance, diabetes mellitus, dyslipidemia, and cardiovascular disease (e.g., atherosclerosis, stroke, myocardial infarction, and heart failure) [1]. Cardiovascular disease is undoubtedly a major cause of death in metabolic disease patients, such as obese subjects [2]. In addition to ischemic heart disease, the state of obesity impairs both the form and function of the myocardium [3,4]. This condition, termed obesity cardiomyopathy, is often characterized by cardiac hypertrophy and impaired contractility (independent of adverse ischemic events) [5,6]. Determining the mechanisms contributing to this non-ischemic heart disease has proven elusive, due to the vast number of neurohumoral alterations in the obesity milieu. These include, but are not exclusive to, dyslipidemia and nutrient excess, chronic over-activation of sympathetic tone and the renin-angiotensin system (RAS), as well as imbalances in paracrine and endocrine factors (e.g., insulin and leptin) [6,7]. At the molecular level, the heart often presents increased reactive oxygen and nitrogen species, elevated lipotoxic species (e.g., ceramide), altered gene and microRNA expression, endoplasmic reticulum (ER) stress, autophagy, disrupted calcium homeostasis, mitochondrial dysfunction, and marked perturbations in metabolic fluxes [1]. The imbalance between nutrient supply, utilization, and clearance that is commonly observed during obesity can lead to death of cells (including cardiomyocytes) [8]. If not corrected, these events can ultimately culminate in the development of dilated cardiomyopathy.

Adipose-derived peptides (*i.e.*, adipokines) are a family of neurohumoral factors that have been implicated not only in the progression/pathogenesis of adiposity and type 2 diabetes mellitus, but in some instances, in the etiology of distinct cardiovascular diseases [9]. For example, circulating levels of adiponectin, an adipokine that markedly improves both insulin sensitivity and cardiac ischemia/reperfusion tolerance, are decreased in obese subjects [10–12]. Similar to adiponectin, a short-lived peptide, termed apelin, has emerged as a novel adipokine that potentially plays a pivotal role in metabolic homeostasis [13]. Due to its high level of expression in adipose tissue, apelin is officially considered an adipokine; however,

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apelin is primarily secreted from endothelial cells (in addition to adipocytes and cardiomyocytes), often acting in a paracrine fashion within numerous organs [14–16]. The apelin gene encodes for a 77 amino acid polypeptide, which is subsequently cleaved to multiple active peptides of 36, 17, 13, and 12 residues in length [17]. The shorter isoforms are believed to possess greatest biological activity, including vasoactive potency [18]. In addition to its actions on the vasculature, apelin exhibits striking metabolic effects, such as stimulation of glucose uptake in skeletal muscle and inhibition of lipolysis in adipose tissue [19,20]. At a molecular level, binding of apelin to the ubiquitously expressed G-protein coupled angiotensin-like receptor 1 (also known as APJ) ultimately leads to activation of various downstream kinases, including AMP-activated protein kinase (AMPK) [13,19,20]. Consistent with a critical role for AMPK in metabolic regulation, genetic deletion of apelin results in glucose intolerance and an insulin resistant state in mice [21]. Conversely, pharmacologic administration of rodents with apelin-13 increases glucose tolerance, and stimulates glucose uptake by both skeletal muscle and adipose tissue [19,22]. In humans, circulating apelin levels appear to be elevated during both obesity and type 2 diabetes mellitus, likely secondary to hyperinsulinemia (as insulin stimulates apelin secretion) [23,24]. Whether elevating apelin levels further in insulin resistant subjects confers therapeutic benefit through improvements in metabolic homeostasis remains an attractive, yet unchallenged possibility.

Experimental observations to date clearly highlight apelin as a potential therapeutic target for distinct cardiometabolic parameters. What is less apparent is the level of cardiovascular benefit conferred by apelin during metabolic diseases. Increasing evidence suggests that apelin has marked beneficial effects on the vasculature, acting as a potent vasodilator, as well as reducing atherosclerosis progression [18,25,26]. Less is known regarding the impact of apelin on the heart, particularly during cardiometabolic disease states. Interestingly, apelin appears to exert cardioprotective effects during ischemic heart disease; several rodent studies have reported improved cardiac ischemia/reperfusion tolerance following apelin treatment (*i.e.*, reduced infarct size and increased contractile function recovery), concomitant with attenuated ER and oxidative stress, decreased mitochondrial permeability transition pore opening, as well as preservation of ATP levels (a marker of energetics) [27–30]. In addition, apelin has been shown to have a positive inotropic influence on the failing myocardium [31]. In addition, Despite recent establishment of links between apelin with metabolic homeostasis and insulin sensitivity, the impact that altered apelin signaling has on the pathogenesis of obesity/diabetic cardiomyopathy is currently known. Similarly, fundamental questions regarding the influence of apelin on basic cardiac processes, such as transcription, signaling, and metabolism, remain largely undefined. In the current issue of the Journal of Molecular and Cellular Cardiology, Ceylan-Isik and colleagues have begun to address these deficiencies [32].

To determine the therapeutic potential of apelin on restoration of cardiac function in an animal model of obesity cardiomyopathy, the current study fed mice a high-fat diet for 6-months, followed by 2-weeks of apelin treatment [32]. The investigators report that this relatively acute pharmacologic intervention was sufficient to normalize cardiac dimensions and contractility, in addition to modest benefits on body weight and glucose tolerance.

Critical to the current study was the finding that the cardiac function benefits seen with apelin treatment were not evident in a separate cohort of untreated mice that were fed in a restricted manner, so that the same level of body weight reduction observed by apelin treatment was achieved. Interestingly, the influence of apelin on cardiac hypertrophy/function appears to be independent of alterations in blood pressure. The current study investigated an impressive number of potential molecular mediators of obesity cardiomyopathy. Of significance, apelin treatment normalized high fat feeding mediated induction of the hypertrophy-related transcription factor GATA4, associated with a dramatic attenuation of cardiomyocyte size, suggesting that apelin may influence cardiac hypertrophy, in part, *via* a transcriptional mechanism. Consistent with improvements in contractility, Ceylan-Isik *et al* investigated changes in calcium handling. Interestingly, apelin was able to normalize high fat diet-induced changes in intracellular Ca^{2+} fluxes and the related regulatory proteins sarco(endo) plasmic reticulum Ca^{2+} -ATPase (SERCA) and phospholamban. These findings suggest that in addition to beneficially influencing hypertrophic growth signaling, apelin also affects calcium handling. In an attempt to define further the molecular mechanisms mediating the cardioprotective effects of apelin, both ER stress and autophagy were investigated. The study reports restoration of BiP levels, suggesting a reduction in high fat feeding-induced ER stress by apelin. Additionally, Atg7 and LC3-II, markers of autophagy, were also normalized by apelin administration. To address the potential direct effects of apelin on cardiomyocytes, as opposed to indirect effects on the milieu during obesity, the investigators performed a series of cell culture based studies; these studies revealed that apelin can directly attenuate palmitate-induced contractile dysfunction in isolated cardiomyocytes.

Collectively, through a comprehensive collection of experimental approaches, Ceylan-Isik *et al* report that 2 weeks of apelin administration is sufficient to normalize chronic high fat feeding-induced obesity cardiomyopathy, at molecular, cellular, and functional levels (summarized in Fig. 1) [32]. Strengths include the complementary use of cell-based *in vitro* studies, suggesting that apelin directly protects cardiomyocytes from fatty acid (palmitate) induced dysfunction (as observed at the level of contractility). Similarly, assessment of a plethora of extracardiac factors (*e.g.*, humoral factors), coupled with a body weight-matched caloric restriction experimental group, is consistent with the concept that the beneficial effects of apelin are not simply secondary to reduced adiposity and/or improvements in the metabolic milieu. These observations therefore lead to obvious questions regarding the mechanisms by which apelin exerts cardioprotection. Although the current study reports normalization of an assortment of biochemical and cellular parameters (*e.g.*, markers of ER-stress, autophagy, and Ca^{2+} handling proteins), establishment of cause-and-effect remains largely unresolved. Accordingly, the mechanism(s) by which apelin ameliorates cardiac hypertrophic growth and contractile dysfunction in the setting of the obesity milieu remain(s) undefined.

Apelin undoubtedly impacts metabolism within peripheral tissues [13,19]. However, whether apelin influences myocardial substrate utilization has not been described previously. The potential significance of such a relationship stems from a growing body of evidence suggesting that when rates of fatty acid uptake are in excess of the rate of fatty acid

oxidation and/or storage (as triglyceride), fatty acyl species are channeled into various 'lipotoxic' pathways (such as ceramide synthesis) in cardiomyocytes, thereby inducing ER and oxidative stress, as well as cellular dysfunction [1,4,33,34]. Given the pivotal role of AMPK (which has been shown to be activated by apelin in distinct cell types) in fatty acid and triglyceride metabolism, it seems likely that apelin influences myocardial substrate utilization [13,20,35]. Indeed, the current study offers indirect evidence in support of this concept. For example, apelin administration reduces myocardial triglyceride levels *in vivo*, while treatment of cardiomyocytes with apelin attenuates palmitate-induced contractile dysfunction *in vitro*. Within the current study, additional limited attempts were made to assess metabolic parameters, including measurement of oxygen consumption in isolated mitochondria, as well as the activity of a β -oxidation enzyme (*i.e.*, β -hydroxyacyl-CoA dehydrogenase). It is important to note that although these *in vitro* measures yielded negative results (*i.e.*, no significant effect of apelin), neither are direct measures of metabolic fluxes in intact cardiomyocytes/hearts. As such, whether apelin-induced modulation of myocardial metabolism contributes to cardioprotection in the setting of high fat feeding remains an unchallenged possibility.

Another dramatic effect of apelin which is worthy of further discussion relates to the rapid reversal of obesity-induced cardiac hypertrophy/remodeling. In the current study, neither chronic high fat feeding nor apelin treatment was found to influence blood pressure [32]. The investigators suggest that apelin-mediated reductions in ER and/or oxidative stress potentially contribute to this beneficial cardiac remodeling. Previous studies in multiple rodent models of obesity and/or insulin resistance suggest that prolonged activation of the local RAS within the heart contributes towards cardiac hypertrophy during metabolic disease states [36,37]. The significance of these findings in relation to the current study is appreciated by reports of an apparent antagonistic relationship between the RAS and apelin. Indeed, it has been suggested that APJ receptors are capable of heterodimerizing with AT1 receptors, thus decreasing signaling through the latter [26]. Interestingly, both apelin and APJ levels are decreased in the failing myocardium [38], raising the question as to whether this augments increased RAS activity during cardiac disease states. Conversely, whether apelin administration is capable of improving contractile function of the diseased heart is an attractive therapeutic question, one that was recently addressed in heart failure patients, yielding positive outcomes [39].

In summary, Ceylan-Isik and colleagues have highlighted the therapeutic potential of apelin in an animal model of metabolic disease-induced cardiac dysfunction. In addition to its established beneficial impact on metabolic homeostasis, this study revealed apelin's ability to rapidly normalize cardiac remodeling and contractile function in the setting of obesity. Although several fundamental questions remain unanswered regarding the mechanisms by which apelin influences cardiac form and function, the novel observations included in the current study, coupled with recent reports of prolonged APJ agonism efficacy in heart failure subjects, highlight apelin as a potential therapeutic target for obesity cardiomyopathy.

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References

1. Wende AR, Symons JD, Abel ED. Mechanisms of lipotoxicity in the cardiovascular system. *Curr Hypertens Rep.* 2012; 14:517–31. [PubMed: 23054891]
2. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, et al. Heart disease and stroke statistics — 2013 update: a report from the American Heart Association. *Circulation.* 2013; 127:e6–245. [PubMed: 23239837]
3. McGavock JM, Victor RG, Unger RH, Szczepaniak LS. American College of P, the American Physiological S. Adiposity of the heart, revisited. *Ann Intern Med.* 2006; 144:517–24. [PubMed: 16585666]
4. Harmancey R, Wilson CR, Taegtmeyer H. Adaptation and maladaptation of the heart in obesity. *Hypertension.* 2008; 52:181–7. [PubMed: 18574077]
5. Wong C, Marwick TH. Obesity cardiomyopathy: diagnosis and therapeutic implications. *Nat Clin Pract Cardiovasc Med.* 2007; 4:480–90. [PubMed: 17712361]
6. Abel ED, Litwin SE, Sweeney G. Cardiac remodeling in obesity. *Physiol Rev.* 2008; 88:389–419. [PubMed: 18391168]
7. Wong C, Marwick TH. Obesity cardiomyopathy: pathogenesis and pathophysiology. *Nat Clin Pract Cardiovasc Med.* 2007; 4:436–43. [PubMed: 17653116]
8. Brindley DN, Kok BP, Kienesberger PC, Lehner R, Dyck JR. Shedding light on the enigma of myocardial lipotoxicity: the involvement of known and putative regulators of fatty acid storage and mobilization. *Am J Physiol Endocrinol Metab.* 2010; 298:E897–908. [PubMed: 20103741]
9. Waki H, Tontonoz P. Endocrine functions of adipose tissue. *Annu Rev Pathol.* 2007; 2:31–56. [PubMed: 18039092]
10. Yamauchi T, Kamon J, Waki H, Terauchi Y, Kubota N, Hara K, et al. The fat-derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity. *Nat Med.* 2001; 7:941–6. [PubMed: 11479627]
11. Shibata R, Sato K, Pimentel DR, Takemura Y, Kihara S, Ohashi K, et al. Adiponectin protects against myocardial ischemia-reperfusion injury through AMPK- and COX-2-dependent mechanisms. *Nat Med.* 2005; 11:1096–103. [PubMed: 16155579]
12. Arita Y, Kihara S, Ouchi N, Takahashi M, Maeda K, Miyagawa J, et al. Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. *Biochem Biophys Res Commun.* 1999; 257:79–83. [PubMed: 10092513]
13. Xu S, Tsao PS, Yue P. Apelin and insulin resistance: another arrow for the quiver? *J Diabetes.* 2011; 3:225–31. [PubMed: 21631898]
14. Kleinz MJ, Davenport AP. Immunocytochemical localization of the endogenous vasoactive peptide apelin to human vascular and endocardial endothelial cells. *Regul Pept.* 2004; 118:119–25. [PubMed: 15003827]
15. Glassford AJ, Yue P, Sheikh AY, Chun HJ, Zarafshar S, Chan DA, et al. HIF-1 regulates hypoxia- and insulin-induced expression of apelin in adipocytes. *Am J Physiol Endocrinol Metab.* 2007; 293:E1590–6. [PubMed: 17878221]
16. Kleinz MJ, Skepper JN, Davenport AP. Immunocytochemical localisation of the apelin receptor, APJ, to human cardiomyocytes, vascular smooth muscle and endothelial cells. *Regul Pept.* 2005; 126:233–40. [PubMed: 15664671]
17. Tatemoto K, Hosoya M, Habata Y, Fujii R, Kakegawa T, Zou MX, et al. Isolation and characterization of a novel endogenous peptide ligand for the human APJ receptor. *Biochem Biophys Res Commun.* 1998; 251:471–6. [PubMed: 9792798]
18. Tatemoto K, Takayama K, Zou MX, Kumaki I, Zhang W, Kumano K, et al. The novel peptide apelin lowers blood pressure via a nitric oxide-dependent mechanism. *Regul Pept.* 2001; 99:87–92. [PubMed: 11384769]

19. Dray C, Knauf C, Daviaud D, Waget A, Boucher J, Buleon M, et al. Apelin stimulates glucose utilization in normal and obese insulin-resistant mice. *Cell Metab.* 2008; 8:437–45. [PubMed: 19046574]
20. Yue P, Jin H, Xu S, Aillaud M, Deng AC, Azuma J, et al. Apelin decreases lipolysis via G(q), G(i), and AMPK-Dependent Mechanisms. *Endocrinology.* 2011; 152:59–68. [PubMed: 21047945]
21. Yue P, Jin H, Aillaud M, Deng AC, Azuma J, Asagami T, et al. Apelin is necessary for the maintenance of insulin sensitivity. *Am J Physiol Endocrinol Metab.* 2010; 298:E59–67. [PubMed: 19861585]
22. Higuchi K, Masaki T, Gotoh K, Chiba S, Katsuragi I, Tanaka K, et al. Apelin, an APJ receptor ligand, regulates body adiposity and favors the messenger ribonucleic acid expression of uncoupling proteins in mice. *Endocrinology.* 2007; 148:2690–7. [PubMed: 17347313]
23. Li L, Yang G, Li Q, Tang Y, Yang M, Yang H. Changes and relations of circulating visfatin, apelin, and resistin levels in normal, impaired glucose tolerance, and type 2 diabetic subjects. *Exp Clin Endocrinol Diabetes.* 2006; 114:544–8. [PubMed: 17177135]
24. Soriguer F, Garrido-Sanchez L, Garcia-Serrano S, Garcia-Almeida JM, Garcia-Arnes J, Tinahones FJ, et al. Apelin levels are increased in morbidly obese subjects with type 2 diabetes mellitus. *Obes Surg.* 2009; 19:1574–80. [PubMed: 19756893]
25. Lv D, Li H, Chen L. Apelin and APJ, a novel critical factor and therapeutic target for atherosclerosis. *Acta Biochim Biophys Sin.* 2013; 45:527–33. [PubMed: 23588025]
26. Chun HJ, Ali ZA, Kojima Y, Kundu RK, Sheikh AY, Agrawal R, et al. Apelin signaling antagonizes Ang II effects in mouse models of atherosclerosis. *J Clin Invest.* 2008; 118:3343–54. [PubMed: 18769630]
27. Tao J, Zhu W, Li Y, Xin P, Li J, Liu M, et al. Apelin-13 protects the heart against ischemia-reperfusion injury through inhibition of ER-dependent apoptotic pathways in a time-dependent fashion. *Am J Physiol Heart Circ Physiol.* 2011; 301:H1471–86. [PubMed: 21803944]
28. Pisarenko OI, Shulzhenko VS, Pelogeikina Iu A, Studneva IM, Kkhatri DN, Beshpalova Zh ZhD. Effects of exogenous apelin-12 on functional and metabolic recovery of isolated rat heart after ischemia. *Kardiologiia.* 2010; 50:44–9. [PubMed: 21118179]
29. Simpkin JC, Yellon DM, Davidson SM, Lim SY, Wynne AM, Smith CC. Apelin-13 and apelin-36 exhibit direct cardioprotective activity against ischemia-reperfusion injury. *Basic Res Cardiol.* 2007; 102:518–28. [PubMed: 17694254]
30. Zeng XJ, Zhang LK, Wang HX, Lu LQ, Ma LQ, Tang CS. Apelin protects heart against ischemia/reperfusion injury in rat. *Peptides.* 2009; 30:1144–52. [PubMed: 19463748]
31. Berry MF, Pirololi TJ, Jayasankar V, Burdick J, Morine KJ, Gardner TJ, et al. Apelin has in vivo inotropic effects on normal and failing hearts. *Circulation.* 2004; 110:II187–93. [PubMed: 15364861]
32. Ceylan-Isik AF, Kandadi MR, Xu X, Hua Y, Chicco AJ, Ren J. Apelin administration ameliorates high fat diet-induced cardiac hypertrophy and contractile dysfunction. *J Mol Cell Cardiol.* 2013 this issue.
33. Borradaile N, Han X, Harp J, Gale S, Ory D, Schaffer J. Disruption of endoplasmic reticulum structure and integrity in lipotoxic cell death. *J Lipid Res.* 2006; 47:2726–37. [PubMed: 16960261]
34. Young M, McNulty P, Taegtmeyer H. Adaptation and maladaptation of the heart in diabetes: Part II: potential mechanisms. *Circulation.* 2002; 105:1861–70. [PubMed: 11956132]
35. Dolinsky VW, Dyck JR. Role of AMP-activated protein kinase in healthy and diseased hearts. *Am J Physiol Heart Circ Physiol.* 2006; 291:H2557–69. [PubMed: 16844922]
36. Alonso-Galicia M, Brands MW, Zappe DH, Hall JE. Hypertension in obese Zucker rats. Role of angiotensin II and adrenergic activity. *Hypertension.* 1996; 28:1047–54. [PubMed: 8952595]
37. Abel ED. Myocardial insulin resistance and cardiac complications of diabetes. *Curr Drug Targets Immune Endocr Metabol Disord.* 2005; 5:219–26. [PubMed: 16089356]
38. Foldes G, Horkay F, Szokodi I, Vuolteenaho O, Ilves M, Lindstedt KA, et al. Circulating and cardiac levels of apelin, the novel ligand of the orphan receptor APJ, in patients with heart failure. *Biochem Biophys Res Commun.* 2003; 308:480–5. [PubMed: 12914775]

39. Barnes GD, Alam S, Carter G, Pedersen CM, Lee KM, Hubbard TJ, et al. Sustained cardiovascular actions of APJ agonism during renin-angiotensin system activation and in patients with heart failure. *Circ Heart Fail.* 2013; 6:482–91. [PubMed: 23519586]

Fig. 1.

Schematic summary of changes related to obesity-associated cardiomyopathy and apelin administration. Obesity is associated with a number of changes in circulating metabolites that impact signaling pathways leading to a disruption of cellular function and the development of cardiomyopathy. The study by Celan-Isik *et al* supports a central role for apelin treatment in the reversal of obesity-induced cardiac dysfunction. SR = sarcoplasmic reticulum; ER = endoplasmic reticulum; RAS = renin-angiotensin system; NO = nitric oxide; TAG = triglyceride. Red = changes associated with obesity; Green = changes following apelin treatment; and ? = unchallenged endpoints. See text for further description. Figure was produced using Servier Medical Art (www.servier.com).