

Abstracts and Commentaries: A new link between obesity and heart disease

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Adipocyte Fatty Acid-Binding Protein Suppresses Cardiomyocyte Contraction. A New Link Between Obesity and Heart Disease

Lamounier-Zepter V, Look C, Alvarez J, et al. *Circ. Res.* 2009;105:326-334.

Obesity is a major risk factor in the development of the metabolic syndrome and cardiovascular diseases, and seems to be directly related to heart failure independently of other risk factors. Indeed, a direct relationship between increased body mass index and increased risk for heart failure has been demonstrated. Several potential mechanisms are under discussion to explain this correlation, including hemodynamic changes with cardiac overload and left ventricular remodeling, and lipid accumulation into the myocardium, leading to lipoapoptosis in cardiomyocytes. These mechanisms, however, do not fully explain the development of heart dysfunction in obese individuals. Adipocytes are known to produce and release a wide variety of bioactive molecules into the bloodstream. On the basis of these data, the authors have recently demonstrated that mature human adipocytes release substances that strongly and acutely suppress the contraction of cardiomyocytes by attenuating intracellular Ca^{2+} concentrations. Their previous findings have revealed a hitherto unknown acute depressant effect of adipocyte-derived factors on cardiac contraction, suggesting a new direct role of adipose tissue in the pathogenesis of myocardium dysfunction.

The authors further characterized cardiodepressant activity by fractionating adipocyte secretory products according to molecular weight and proteomic analysis, identifying adipocyte fatty acid-binding protein 4 (FABP4)* as the active agent. FABPs are members of a highly conserved family of cytosolic

proteins showing a high affinity for long-chain fatty acids and other hydrophobic ligands. FABP4 is predominantly expressed in adipose tissue, and accounts for approximately 1% of total cytosolic protein in human adipose tissue. Cytoplasmic FABP4 is involved in trafficking intracellular fatty acids and other lipid signals by interaction with functional targets. In experimental animal models, FABP4 deficiency protects against the development of diabetes and atherosclerotic cardiovascular disease in both genetic and dietary forms of obesity. Humans with a functional genetic variant of the FABP4 gene, resulting in reduced adipose tissue expression of FABP4, have lower serum concentrations of triglycerides, and are at significantly reduced risk for type 2 diabetes and coronary artery disease. In a recent cross-sectional study, a correlation was observed between circulating concentrations of FABP4 and metabolic syndrome. Together, these clinical and experimental data support a key role for FABP4 in the development of metabolic and cardiovascular complications in obesity.

Commentary

This study by Lamounier-Zepter et al has identified FABP4 as a cardiodepressant factor. Human adipocytes in a primary cell culture system released high amounts of FABP4 into the extracellular medium. FABP4 at concentrations similar to those released by the adipocytes acutely inhibited cardiomyocyte contraction. This effect was concentration-dependent and reduced intracellular Ca^{2+} -transient. Recent studies from animal models support a novel role for FABP4 in linking obesity with many features of the metabolic syndrome. Mice lacking FABP4 exhibit a protective phenotype against the development of

insulin resistance associated with genetic or diet-induced obesity. Consistent with these animal studies, a close positive correlation between circulating concentrations of FABP4 and features of the metabolic syndrome has been revealed in humans. On the basis of observations that FABP4 correlates positively with body mass index and fat percentage, and that the murine preadipocyte cell line, 3T3-L1, releases FABP4 into the extracellular medium, adipose tissue has been suggested as being the main source of circulating FABP4. Present findings that human adipocytes in primary cell culture also release FABP4 into the extracellular medium support the role of adipose tissue in the secretion of FABP4 into circulation. Although several studies have pointed to a role of FABP4 in the development of some features of the metabolic syndrome, the pathophysiological mechanisms of circulating FABP4 in mediating the metabolic and cardiovascular complications of obesity remained undetermined.

These are the first research findings to suggest a direct bioactive role of FABP4 in heart function, independently of its role as a transport protein. Interestingly, expression of FABP4 in epicardial adipose tissue has recently been reported, with increased concentrations in patients with metabolic syndrome [1]. Epicardial fat tissue accumulates around the heart and is directly related to intra-abdominal visceral fat and other features of the metabolic syndrome. There are now compelling data pointing to a role of epicardial fat tissue in modulating heart morphology and function. The absence of a fibrous fascial layer between epicardial fat tissue and underlying myocardium permits a close anatomic relationship between both tissues, thus paving the way for factors released from adipocytes to influence myocardial function directly. Consequently, the FABP4 expression found in epicardial fat tissue supports the hypo-

thesis of a direct paracrine effect exerted by FABP4 on the development of heart dysfunction in patients with obesity and metabolic syndrome. In addition, the increase in circulating FABP4 released from subcutaneous and/or visceral adipose tissue in obese individuals could mediate heart dysfunction in those individuals. FABP4 acutely depressed shortening amplitude as well as intracellular systolic peak Ca^{2+} in a dose-dependent manner in isolated rat cardiomyocytes. The heart-specific FABP isoform (FABP3) revealed a similar cardiodepressant effect. It was possible to identify the N-terminal amino acids 1–20 of FABP4 as the most effective cardiodepressant domain. In the absence of any effect of FABP4 on action potential duration and L-type Ca^{2+} current, a reduced excitation–contraction gain caused by FABP4 appears to be the most probable inhibitory mechanism. Both FABP4 and FABP3 are effective in the extracellular medium, thus suggesting a surface receptor for heart and adipocyte FABP. Furthermore, the heart FABP isoform selectively binds to a high-affinity plasma membrane receptor on cardiomyocytes.

In conclusion, these novel data show that FABP4 is released from human adipocytes and elicits a direct and acute Ca^{2+} -dependent suppressing effect on cardiomyocyte contraction. The increased concentrations of circulating FABP4 and/or locally expressed FABP4 in epicardial fat tissue as observed in obese individuals may be partially responsible for the development of heart dysfunction in these individuals.

*see glossary for definition of this term. ■

REFERENCE

1. Vural B, Atalar F, Ciftci C, et al. Presence of fatty-acid-binding protein 4 expression in human epicardial adipose tissue in metabolic syndrome. *Cardiovasc Pathol*. 2008;17:392–398.