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A new role for the natriuretic peptides: Metabolic regulators of the adipocyte

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The heart and adipose tissue are both endocrine organs, and there is increasing evidence for cross-talk between them although precise mechanisms remain poorly defined. Of particular importance is the role that such cross-talk could play in both total body metabolism and cardiac metabolism. The timely and thought-provoking article by Tsukamoto and colleagues in this issue adds to this body of knowledge by examining both *in vitro* and *in vivo* the biological actions of cardiac natriuretic peptides on adiponectin production and secretion (1).

By now the cardiovascular community is well aware that atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP) promote vasodilatation, natriuresis, improve diastolic function, suppress aldosterone, and inhibit cardiac hypertrophy and fibrosis (2,3). Less well-known is that ANP and BNP have metabolic roles, specifically ANP and BNP are lipolytic and slow gastric emptying and absorption (4,5). Indeed the binding of ANP or BNP to the NPR-A receptor, which is present in adipocytes, results in production of the second messenger cGMP. The cGMP in turn activates protein kinase G, leading to phosphorylation of hormone sensitive lipase (HSL). The HSL is thus activated and hydrolysis of fatty acids ultimately occurs (4,6). ANP has also been shown to induce post-prandial lipid oxidation in humans (7). These lipolytic actions of ANP and BNP, which are generally assumed to be primate-specific, underscore an emerging role for the heart in human metabolism (8). This has caused speculation as to the potential role of chronic, pathological BNP elevation in cardiac cachexia (9). Conversely, plasma BNP and NT-proBNP levels are depressed in obese patients as compared to lean patients despite having higher left ventricular end diastolic pressures. This has led to the conjecture that decreased natriuretic peptide concentrations in the obese are secondary to a relative decreased myocardial synthesis or impaired release from the cardiomyocytes (10). Indeed, this suppression of ANP and BNP in obesity could, based upon the cardiorenal and metabolic properties of ANP and BNP, contribute to clinical phenotypes associated with the metabolic syndrome. Furthermore, the newly appreciated metabolic properties these two cardiac hormones may suggest a novel therapeutic target in metabolic diseases such as obesity.

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Adiponectin, a 244 amino acid peptide that is known to self-associate to form multimers, was first described in 1995 and is also emerging as an important regulator of metabolism (11-14). Adiponectin is primarily, if not exclusively, thought to be produced by adipocytes although some studies have shown that cardiomyocytes produce low levels of adiponectin and that there is a significant step-up of adiponectin levels in the coronary sinus compared to the aortic root in heart failure (HF) patients suggesting that there may be cardiac release of adiponectin in HF patients (15,16). Despite the fact that adiponectin is primarily produced by adipose tissue, there seems to be an almost paradoxical relationship between adiponectin plasma concentrations and BMI. Indeed, it is well established that in humans plasma adiponectin levels are inversely related to body mass index (BMI) and per cent body fat (17). Plasma adiponectin concentrations are low in the obese, in diabetics and in the setting of insulin resistance, and in coronary atherosclerotic disease (18-20). In contrast, plasma adiponectin levels are high in individuals with anorexia nervosa and in HF patients with cachexia (21-23). Furthermore, the administration of exogenous adiponectin to animals resulted in weight loss (24).

Prior studies have found a positive correlation between adiponectin and NT-proBNP or BNP levels in HF patients and in normal individuals (23,25,26). Weight loss after bariatric surgery has been shown to result in increased adiponectin as well as BNP and NT-proBNP levels (27,28). It has also been shown in a small clinical study that decompensated HF patients who received ANP infusions had increased plasma levels of total and high molecular weight (multimeric) adiponectin (29).

With all of this background, the work of Tsukamoto and colleagues featured in this issue adds mechanistic insights. Importantly, the authors demonstrated that ANP and BNP via the cGMP pathway increase adiponectin mRNA expression and adiponectin secretion form cultured adipocytes. How this functionally impacts HF is still unclear, although these authors and others have speculated that, in the setting of HF, adiponectin secretion may occur to attenuate the chronic energy deprivation the heart faces as it switches from predominantly fatty acid oxidation to glucose oxidation (1,15,23). Also, the natriuretic peptide induced lipolysis and adiponectin secretion could aid in weight loss, which in the setting of heart failure could be considered a cardiac unloading action. An extreme form of this could be cardiac cachexia. Clearly there is a need for further work in this fascinating area.

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