Cardiac Natriuretic Peptides: Contributors to Cardiac Cachexia or Possible Anti-obesity Agents or Both?

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The cardiac natriuretic peptides (NPs) atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP) are both secreted by the heart in response to myocardial stress and stretch and act via binding to guanylyl cyclase-A (GC-A), with subsequent generation of the second messenger cyclic guanosine monophosphate. GC-A is widely expressed in mannnals, e.g., in heart, kidney, vascular smooth muscle, skeletal muscle, adipose tissue, liver, stomach, terminal ileum, lung, adrenals, and brain. Consequently, the NPs have pleiotropic actions, many of which can be considered to unload the heart, specifically vasodilation, natriuresis, and inhibition of the renin-angiotensin-aldosterone system (1). Vila et al. (2) in the current issue of Diabetes present important information on the emerging metabolic actions of GC-A activation, specifically on its hunger and ghrelin suppressing actions (Fig. 1).

Obesity, insulin resistance, and the metabolic syndrome have all been associated with reduced NP levels (3,4). The low level of NPs seen in obesity is at least in part due to decreased cardiac secretion and, in fact, cardiac NP levels have been shown to increase after bariatric surgery (5–7).

Thus, obesity, insulin resistance/type 2 diabetes (T2DM), and the metabolic syndrome may represent states of NP deficiency. Could GC-A agonists be useful in the treatment of metabolic disease? Available evidence suggests that the net effects of NP administration in these settings may vary depending upon duration of exposure to the extraneous NP and the study model used. Sengènes et al. (8,9) demonstrated that ANP and BNP are part of a lipolytic pathway that uses hormone-sensitive lipase and is independent of catecholamines. Birkenfeld et al. (10) demonstrated that in postprandial humans, acute infusion of ANP also stimulated lipid oxidation—but to a lesser degree than the associated stimulation of lipolysis. Such excess lipolysis would contribute to ectopic deposition of fat in organs such as the heart and liver and could reduce insulin sensitivity. However, it is unknown whether more chronic GC-A activation would also raise such concerns. Indeed, recent preclinical studies suggest that chronic GC-A agonism may hold potential in obesity and the metabolic syndrome. BNP transgenic mice have increased fat oxidation and skeletal muscle mitochondrial biogenesis and are protected against diet-induced obesity (11). Also fascinating is the finding that the NPs may increase energy expenditure by inducing a brown fat thermogenic program in white adipose tissue (12).

There have also been some studies on GC-A activation and glucose metabolism. BNP transgenic mice have lower glucose and insulin levels and improved glucose tolerance compared with wild-type mice (11). Human genetic association studies have found that the minor allele of the BNP single nucleotide polymorphism rs1983889 is associated not only with higher BNP levels but also with lower blood glucose levels and lower prevalence of T2DM (13). Similarly, humans with low plasma ANP levels were more likely to develop T2DM, whereas a high NP genotype was associated with reduced body weight and incidence of the metabolic syndrome (14,15). Acute administration of BNP to healthy subjects lowered plasma glucose concentrations after glucose loading without affecting β-cell function or insulin sensitivity (16). This may be secondary to an increase in the volume of distribution of the glucose or to increased renal excretion (16,17).

The current study by Vila et al. (2) represents a start in evaluating the appetite-regulating effects of GC-A agonism. In this single-blind crossover study, intravenous BNP or placebo was given for 4 h to 10 healthy young males with normal BMIs. The effects of BNP on ghrelin (total and acylated), adiponectin, PYY, subjective measures of hunger and satiety by visual analog scale, plasma glucagon-like peptide 1, oxyntomodulin, pancreatic peptide, and leptin were evaluated. Relative to placebo, BNP significantly decreased total ghrelin and decreased the fasting-induced increase in acylated ghrelin. BNP also significantly decreased hunger and increased satiety. No significant effects were found in any of the other hormones (2).

In general, this is a straightforward study, a strength of which is the crossover design. A double-blind design would have been preferable to exclude any potential effect of the unblinded investigator to influence the subjects' assessment of appetite and satiety. However, it is unlikely that humoral factors such as ghrelin would be affected by this single-blind design. Of note, all of the subjects in the current study were healthy and had normal BMIs. It will be of interest to test whether similar results will be obtained in obese subjects, as they have decreased BNP levels. As the authors mention, their adiponectin results are at variance with what has been previously seen in vitro and in vivo in patients with heart failure (HF) (18). The reasons for this are unclear, but the disease status may play a role. Finally, the authors report that the levels of BNP immunoreactivity achieved with the BNP infusion were in the range seen in HF patients (400–500 pg/mL). However, it should be noted that a substantial proportion of the BNP immunoreactivity measured in HF may consist of the less bioactive prohormone, the 189-amino acid proBNP, or enzymatically cleaved derivatives of BNP (19,20). Thus, the study subjects are likely to have received more...
bioactive BNP than HF patients with the same corresponding levels of BNP plasma immunoreactivity.

Where do we go from here? The general impression is that GC-A activation tends to promote lower weight, less calorie intake, and catabolism. In cardiac cachexia, which is associated with increased mortality, this would not be desirable (even though weight loss to a lesser degree could be considered a “cardiac unloading” action). However, given the apparent reduced bioactivity of the circulating NPs in advanced HF, it is unclear to what extent the NPs are actually responsible for cardiac cachexia, especially given other potential causal factors, such as inflammation. Furthermore, the BNP transgenic mice mentioned above did not have a cachectic phenotype, suggesting that increased GC-A activation per se does not cause cachexia (11). What may be most interesting is the potential benefit the obese or patients with diabetes may derive from chronic NP supplementation. Therefore, studies are required to assess the net effect of chronic GC-A activation in humans.

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REFERENCES
1. Potter LR. Regulation and therapeutic targeting of peptide-activated receptor guanylyl cyclases. Pharmacol Ther 2011;130:71–82
2. Vila G, Grimm G, Resl M, et al. B-type natriuretic peptide modulates ghrelin, hunger, and satiety in healthy men. Diabetes 2012;61:2592–2596
3. Khan AM, Cheng S, Magnusson M, et al. Cardiac natriuretic peptides, obesity, and insulin resistance: evidence from two community-based studies. J Clin Endocrinol Metab 2011;96:3243–3249
4. Wang TJ, Larson MG, Keyes MJ, Levy D, Benjamin EJ, Vasan RS. Association of plasma natriuretic peptide levels with metabolic risk factors in ambulatory individuals. Circulation 2007;115:1345–1353
5. Taylor JA, Christenson RH, Rao K, Jorge M, Gottlieb SS. B-type natriuretic peptide and N-terminal pro B-type natriuretic peptide are depressed in obesity despite higher left ventricular end diastolic pressures. Am Heart J 2006;152:1071–1076
6. Wang TJ, Larson MG, Levy D, et al. Impact of obesity on plasma natriuretic peptide levels. Circulation 2004;109:594–600
7. Chen-Tournoux A, Khan AM, Bagghish AL, et al. Effect of weight loss after weight loss surgery on plasma N-terminal pro-B-type natriuretic peptide levels. Am J Cardiol 2010;106:1450–1455
8. Sengenés C, Berlan M, De Glisezinski I, Lafontan M, Galitzky J. Natriuretic peptides: a new lipolytic pathway in human adipocytes. FASEB J 2000;14:1345–1351
9. Sengenés C, Bouloumie A, Hauner H, et al. Involvement of a cGMP-dependent pathway in the natriuretic peptide-mediated hormone-sensitive lipase phosphorylation in human adipocytes. J Biol Chem 2003;278:48617–48626
10. Birkenfeld AL, Budziarek P, Boschi-Muller M, et al. Atrial natriuretic peptide induces postprandial lipid oxidation in humans. Diabetes 2008;57:1199–1204
11. Miyashita K, Itoh H, Tsujimoto H, et al. Natriuretic peptides/cGMP/cGMP-dependent protein kinase cascades promote muscle mitochondrial biogenesis and prevent obesity. Diabetes 2005;54:2880–2892
12. Bordicchia M, Liu D, Amri EZ, et al. Cardiac natriuretic peptides act via p38 MAPK to induce the brown fat thermogenic program in mouse and human adipocytes. J Clin Invest 2012;122:1022–1036
13. Meirhaeghe A, Sandhu MS, McCarthy MI, et al. Association between the T-381C polymorphism of the brain natriuretic peptide gene and risk of type 2 diabetes in human populations. Hum Mol Genet 2007;16:1343–1350
14. Magnusson M, Jucic A, Hedblad B, et al. Low plasma level of atrial natriuretic peptide predicts development of diabetes: the prospective Malmo Diet and Cancer study. J Clin Endocrinol Metab 2012;97:638–645
15. Cannone V, Boerigter G, Cataliotti A, et al. A genetic variant of the atrial natriuretic peptide gene is associated with cardiometabolic protection in the general community. J Am Coll Cardiol 2011;58:629–636
16. Heinisch BB, Vila G, Resl M, et al. B-type natriuretic peptide (BNP) affects the initial response to intravenous glucose: a randomised placebo-controlled cross-over study in healthy men. Diabetologia 2012;55:1400–1405
17. Welsh P, McMurray JJ. B-type natriuretic peptide and glycaemia: an emerging cardiometabolic pathway? Diabetologia 2012;55:1240–1243
18. Tsukamoto O, Fujita M, Kato M, et al. Natriuretic peptides enhance the production of adiponectin in human adipocytes and in patients with chronic heart failure. J Am Coll Cardiol 2009;53:2070–2077
19. Dries DL, Ky B, Wu AH, Rame JE, Putt ME, Cappola TP. Simultaneous measurement of unprocessed Pro-BNP1–108 in addition to processed BNP32 improves identification of high-risk ambulatory patients with heart failure. Circ Heart Fail 2010;3:220–227
20. Niederkofler EE, Kierman UA, O’Rear J, et al. Detection of endogenous B-type natriuretic peptide at very low concentrations in patients with heart failure. Circ Heart Fail 2008;1:258–264
21. Addisu A, Gower WR Jr, Landon CS, Dietz JR. B-type natriuretic peptide decreases gastric emptying and absorption. Exp Biol Med (Maywood) 2008;233:475–482