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 mammals, 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. Sengenès 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 rs198389 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 108-amino acid proBNP, or enzymatically cleaved derivatives of BNP (19,20). Thus, the study subjects are likely to have received more

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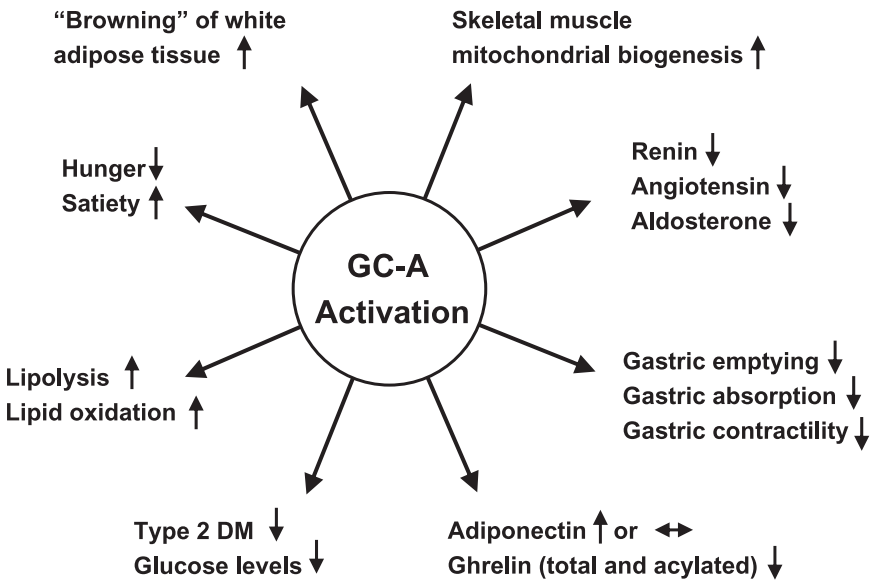

FIG. 1. Potential effects of GC-A activation on metabolism and energy balance. There is emerging evidence from animal and human studies that GC-A activation by natriuretic peptides may modulate metabolism and energy balance. See text for details and Addisu et al. (21) for a study on gastric emptying.

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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