ANP-ing Up Diabetes: Impaired Natriuretic Peptide Action in Muscle Forms a Mechanistic Link Between Obesity and Diabetes

A growing body of work concerns the role of natriuretic peptides (NPs) in metabolism and insulin sensitivity, the latest addition to which is published in this issue of Diabetes (1). Three principal structurally related NPs exist in mammals: atrial natriuretic peptide (ANP), produced primarily by the cardiac atria; brain/B-type natriuretic peptide (BNP), secreted by the ventricle and brain; and C-type natriuretic peptide (CNP), originating from the vascular endothelium, central nervous system, and kidney. They were originally shown to possess potent natriuretic, diuretic, and vasodilatory activity, thus playing a significant role in the prevention of circulatory volume overload and hypertension. These peptides use plasma membrane–situated natriuretic peptide receptors (NPRs) A and B, with the A receptor showing a preference for ANP and BNP and the B receptor being specific for CNP, while a distinct C receptor is responsible for peptide clearance in tissues. Binding of peptides to NPRA leads to the activation of intracellular cyclic guanosine monophosphate (cGMP)-dependent signaling cascades involving cGMP-dependent protein kinases, phosphodiesterases, and ion channels that mediate the physiological effects of NPs (reviewed in ref. 2).

Recently, parallel metabolic actions of NPs have been demonstrated in adipose tissue, with selective effects in the visceral adipose depot, expansion of which is most associated with insulin resistance (IR). ANP-stimulated cGMP-mediated phosphorylation of hormone-sensitive lipase results in lipolysis in primates/humans that is independent of β-adrenergic stimulation (3–5), thereby inhibiting visceral adipocyte hypertrophy (6). In addition, ANP treatment causes reduced adipose secretion of proinflammatory cytokines and increased secretion of the insulin-sensitizing adipokine adiponectin (7), while BNP infusion induces “browning” of white adipose tissue and thus increased energy expenditure (8), both effects that would be likely to ameliorate IR. Furthermore, cross-sectional studies of large cohorts showed associations between reduced plasma NPs and both obesity and IR (9–11), while low plasma ANP also predicts the subsequent development of type 2 diabetes (T2D) (12). The combination of reduced cardiac NP secretion and/or increased clearance in obesity has been termed the “natriuretic handicap” (13).

However, not only is visceral adiposity an independent determinant of plasma BNP in healthy individuals, but so is muscle mass (14). In addition, NPRA is upregulated in the muscle from exercise-trained individuals (15), implying that muscle may also functionally adapt in response to NPs released from the exercising heart. The metabolic effects of NPs in the muscle are starting to be elucidated and could be of importance for diabetes, given that this tissue is responsible for the majority of insulin-stimulated glucose disposal. Mice with genetically induced increases in plasma BNP or cGMP-dependent protein kinase activity demonstrate reduced fat depot size after being fed a high-fat diet (HFD), accompanied by reduced ectopic lipid deposition in the liver and muscle, owing to increased mitochondrial content and fat oxidation (16). Moreover, NP-induced increases of mitochondrial fat oxidation and/or uncoupling have been shown in cultured human muscle cells (15), while BNP infusion can also protect against mitochondrial dysfunction and oxidative stress in the muscle (17). However, to date, the mechanisms whereby obesity-induced impairment in the NP axis might lead to the development of T2D have not been elucidated.

In this issue of Diabetes, Coué et al. (1) describe a series of studies in which they investigate whether altered NP action in the muscle might mediate the natriuretic

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handicap and link obesity with diabetes. Initially, they analyzed the protein expression of each NPR in muscle biopsies from human volunteers with varying degrees of body fat, obesity, impaired glucose tolerance, or T2D. Muscle NPRA protein levels were correlated directly with insulin sensitivity and inversely with the degree of adiposity in healthy volunteers, were reduced in obese subjects, but were increased in response to diet-induced weight loss. Conversely, NPRC was increased in obese individuals with impaired glucose tolerance or T2D, implying overall that NP action is likely to be impaired in the muscle of obese or IR people (Fig. 1). The authors then investigated the physiological significance of these changes by studying HFD-fed and leptin receptor–deficient obese and diabetic db/db mice, which demonstrated consistent reductions in muscle NPRA (both models), upregulation of NPRC (latter model), and impaired phosphorylation of p38 mitogen-activated protein kinase, a key downstream signaling intermediate (both models). Acute infusion of BNP did not affect glucose homeostasis, consistent with a lack of effect of acute NP treatment of primary human muscle cells on glucose uptake. However, rescue of the natriuretic handicap by administration of BNP to HFD-fed or db/db mice for 4 weeks resulted in improved glucose tolerance and insulin responsiveness, without altering plasma insulin levels. These effects are accompanied by reduced accumulation of the toxic lipid intermediates ceramide and diacylglycerol, improved insulin signaling, and mitochondrial fat oxidation in muscle. Interestingly, however, comparable effects are not observed in either liver or adipose tissue. Following this up in cultured human myotubes, the authors showed similar effects to those seen in mice. Whereas there were no acute effects of BNP on lipid metabolism, 3 days of treatment led to reduced accumulation of lipids, including ceramide, and increased fatty acid oxidation. Thus, in summary, the authors present evidence that NPs have a role in maintaining muscle insulin sensitivity through limiting obesity-related local accumulation of lipotoxic intermediates and that this mechanism is impaired in T2D. Further work must identify the key components of the signaling pathways involved in this mechanism.

Other recently published works have suggested that the NP axis could be involved in mediating the effects of obesity therapies, as improved NP sensitivity was demonstrated alongside adipose tissue browning as part of the beneficial effect of bariatric surgery in a rodent model (18) and increased ANP release and decreased clearance was involved in the effects of exercise in human subjects (19). The study by Coué et al. (1) further implies that overcoming the natriuretic handicap in the muscle could be a viable approach for the treatment of T2D. Given that heart disease/hypertension and T2D are frequent lifestyle-related comorbidities and infusion of NPs can be used to treat the former, targeting of NPRs may have promise as a future therapeutic approach for a significant subset of patients. However, NP infusions represent an

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Figure 1 — Summary of NP action in the skeletal muscle in healthy individuals (A) and obese individuals with diabetes (B). NPs circulate in reduced concentrations in obese individuals with diabetes compared with the levels in healthy individuals. Furthermore, expression of NPRA, which binds NPs and activates intracellular signaling events, is reduced, while expression of NPRC, which clears NPs in tissues, is increased in obesity and T2D. In healthy individuals, generation of cGMP from guanosine triphosphate (GTP) by the guanylyl cyclase activity of NPRA activates a signaling pathway resulting in the phosphorylation (P) and activation of p38 mitogen-activated protein kinase (p38 MAPK) and the increased transcription of peroxisome proliferator–activated receptor coactivator γ-1α (PGC1α). This is associated with mitochondrial biogenesis and oxidation of lipids, including the lipotoxic diacylglycerols (DAGs) and ceramides. In obese individuals, NP signaling from NPRA is attenuated, predisposing to DAG and ceramide accumulation in the muscle and thus IR, characterized by inhibition of insulin signaling via Akt and impaired glucose disposal.
impractical means of treating diabetes chronically, and it remains to be seen whether drugs targeting NPRs or downstream signaling pathways will be developed and proven to be effective in breaking the link between obesity and T2D.

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References