ANP-ing up diabetes: impaired natriuretic peptide action in muscle forms a mechanistic link between obesity and diabetes

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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 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 utilise plasma membrane-situated natriuretic peptide receptors (NPR) A and B, with the A receptor showing 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 activation of intracellular cGMP-dependent signalling cascades involving cGMP-dependent protein kinases, phosphodiesterases and ion channels that mediate the physiological effects of NPs (reviewed in (2)).

Recently, parallel metabolic actions of NPs have also been demonstrated in adipose tissue, with selective effects in the visceral adipose depot, expansion of which is most associated with insulin resistance. ANP-stimulated cGMP-mediated phosphorylation of hormone-sensitive lipase results in lipolysis in primates/humans that is independent of beta-adrenergic stimulation (3-5), thereby inhibiting visceral adipocyte hypertrophy (6). In addition, ANP treatment causes reduced adipose secretion of pro-inflammatory cytokines and increased secretion of the insulin sensitising adipokine adiponectin (7), while BNP infusion induces "browning" of white adipose tissue, and thus increased energy expenditure (8), both of which effects would be likely to ameliorate insulin resistance (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 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 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 both demonstrate reduced fat depot size after high fat diet (HFD) feeding, accompanied by reduced ectopic lipid deposition in liver and muscle, due to increased mitochondrial content and fat oxidation (16). Moreover, NP-induced increases 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 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.

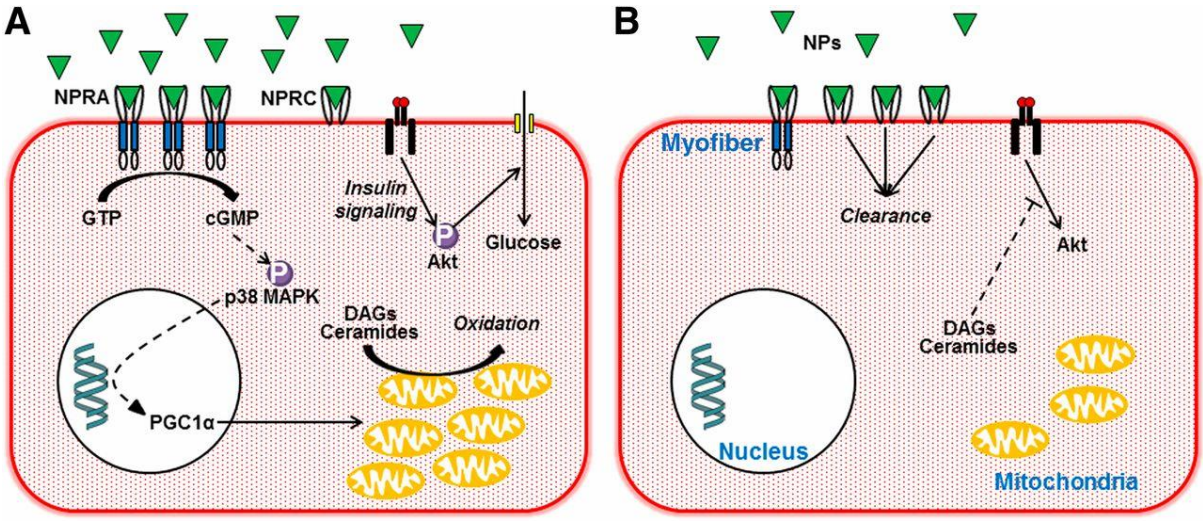
In this issue of *Diabetes*, Coué *et al* describe a series of studies in which they investigate whether altered NP action in muscle might mediate the natriuretic handicap and link obesity with diabetes (1). Initially, they analysed protein expression of each in muscle biopsies from human volunteers with varying degrees of body fat, obesity, impaired glucose tolerance (IGT) 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 increased in response to diet-induced weight loss. Conversely, NPRC was increased in obese individuals with IGT or T2D, implying overall that NP action is likely to be impaired in muscle of obese or insulin resistant people. 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, up-regulation of NPRC in the latter model, and also impaired phosphorylation of p38 mitogen-

activated protein kinase, a key downstream signalling intermediate. 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 four weeks resulted in improved glucose tolerance and insulin responsiveness, without altering plasma insulin levels. These effects were accompanied by reduced accumulation of the toxic lipid intermediates ceramide and diacylglycerol, improved insulin signalling and mitochondrial fat oxidation in muscle. Interestingly, however, comparable effects were 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, three 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 signalling pathways involved in this mechanism.

Other recently published work suggests 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), while increased ANP release and decreased clearance was involved in the effects of exercise in human subjects (19). This new study (1) further implies that overcoming the natriuretic handicap in muscle could be a viable approach for the treatment of T2D. Given that heart disease/hypertension and T2D are frequent lifestyle-related co-morbidities 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 sub-set of patients. However, NP infusions represent an impractical means of treating diabetes chronically and it remains to be seen whether drugs targeting NPRs or downstream signalling pathways will be developed and prove to be effective in breaking the link between obesity and T2D.

Figure legend

Summary of natriuretic peptide action in skeletal muscle in healthy (A) and obese/diabetic (B) individuals



Natriuretic peptides (NPs) circulate in reduced concentrations in obese/diabetic individuals than in healthy individuals. Furthermore, expression of natriuretic peptide receptor A (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 type 2 diabetes. In healthy individuals, generation of cyclic guanosine monophosphate (cGMP) from guanosine triphosphate (GTP) by the guanylyl cyclase activity of NPRA activates a signaling pathway resulting in phosphorylation (P) and activation of p38 mitogen-activated protein kinase (p38 MAPK) and increased transcription of peroxisome proliferator-activated receptor coactivator 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 muscle and thus insulin resistance, characterised by inhibition of insulin signaling via Akt and impaired glucose disposal.

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