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Commentary

Does Insulin Resistance Trigger Natriuretic Peptide Deficiency?

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A number of prospective studies have suggested that obesity and type 2 diabetes (T2D) promote a state of relative natriuretic peptide (NP) deficiency, so-called "natriuretic handicap" (Das et al., 2005; Wang et al., 2004). This observation led to the hypothesis that NP deficiency contributes to the susceptibility of obese individuals to hypertension. Considering that obesity/T2D are characterized by insulin resistance and that insulin resistance is a risk factor of hypertension, it has been proposed that insulin resistance triggers NP deficiency in obesity/T2D (Khan et al., 2011). Insulin resistance defines a pathophysiological state where higher insulin levels are required to maintain blood glucose concentrations in the normal range. Hyperinsulinemia and hyperglycemia in the fasting and postprandial state are common features of obesity and T2D. Researchers therefore assumed that systemic factors from the pro-insulin resistant obese milieu, such as hyperinsulinemia and hyperglycemia, could inhibit atrial proANP expression/secretion. A recent study in cultured human embryonic stem cell-derived cardiomyocytes indicate that glucose down-regulate ANP mRNA levels by inducing miR-425, a negative regulator of its expression (Arora et al., 2016). These findings were comforted by *in vivo* experiments showing a 27% reduction of plasma NT-proANP levels in healthy humans challenged with a high carbohydrate drink. One study in obese subjects also suggested that hyperinsulinemia may contribute to lower levels of NP by up-regulating NP clearance receptor (NPRC) expression in subcutaneous fat tissue (Pivovarova et al., 2012). In light of these observations, hyperglycemia and hyperinsulinemia may be the mechanisms underlying NP deficiency in obesity and T2D. Since T2D is also characterized by elevated blood glucagon levels (Lee et al., 2016), it is not possible to discriminate the specific effect of high glucose levels on ANP secretion independently of insulin and glucagon levels.

In this issue of *EBioMedicine*, Zois et al. (2017-in this issue) aimed to assess this question in a series of clinical studies in healthy individuals with normal and impaired glucose tolerance. In a first experimental study, they examined cardiac ANP secretion by measuring plasma NT-proANP in lean healthy individuals infused with either glucagon alone or in combination with somatostatin while blood glucose levels were clamped. No acute effect of glucagon and somatostatin on cardiac ANP secretion were observed. In a second longitudinal study, they investigated the influence of acute hyperinsulinemia during euglycemic conditions on cardiac ANP secretion before and after a 7-days bed rest (BR). BR induced a significant reduction of plasma NT-proANP levels by 25% and a concomitant state of insulin resistance and glucose intolerance. However no relationship between changes in plasma NT-proANP, the M-value and the Matsuda index was noted. No effect of acute euglycemic hyperinsulinemia was observed before and after the BR. In a third cross-sectional study, Zois et al. (2017-in this issue) assessed the relationship between impaired glucose regulation and circulating NT-proANP levels. Impaired glucose regulation in middle-aged men and women was not associated with changes in plasma NT-proANP despite mild insulin resistance. Together this study highlights that acute changes in plasma insulin and glucagon do not influence cardiac proANP secretion.

These findings challenge in some ways previous work and underpin alternative hypotheses to link insulin resistance and NP deficiency. One first possibility is that NP deficiency requires additional factors than insulin resistance only. This may include hyperglycemia and low-grade inflammation. This hypothesis is supported by a number of studies showing an elevated expression of NPRC at the mRNA and protein level in adipose tissue and skeletal muscle of obese individuals with T2D *versus* lean with normal glucose tolerance (Coue et al., 2015; Ryden et al., 2016). A chronic increase in adipose NPRC expression could trigger a down-regulation of circulating NP levels on the long-term. This is consistent with studies in mouse models of obesity and T2D (db/db mice) where NPRC protein content is up-regulated in fat and muscle tissue and negatively correlates with circulating NP levels (Coue et al., 2015). Another alternative is that NP deficiency occurs at the tissue level before circulating levels are impacted. This also implies that NP deficiency precedes insulin resistance and T2D. This is in line with previous studies demonstrating a down-regulation of NPRA mRNA and protein level in fat tissue and skeletal muscle in obesity and T2D both in humans and mice (Coue et al., 2015; Ryden et al.,

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2016). This is also consistent with prospective studies showing that low circulating levels of NP are predictive of new onset T2D (Lazo et al., 2013).

In summary, insulin resistance does not appear to be causal of NP deficiency. Decreased NT-proANP secretion may occur as a late event in obesity progression. This does not exclude however an early state of NP deficiency characterized by a reduced NP signaling in target tissues. Mouse studies are required to investigate the causal association between NP deficiency and the development of obesity/T2D.

Disclosure

The author declared no conflicts of interest.

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