Diet-induced obesity obstructs insulin signaling in the heart

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INSULIN RESISTANCE OCCURS frequently in people who are overweight or obese. Elucidating the mechanisms responsible for insulin resistance and defining its physiological consequences are highly relevant to understanding human disease. Impaired insulin sensitivity in skeletal muscle and liver are directly responsible for the development of type 2 diabetes (15). Although insulin resistance in other organs does not constitute a disease per se, emerging evidence suggests that it plays a role in the pathogenesis of vascular disease and heart failure. Epidemiological studies have established a strong association between insulin resistance and an increased risk for myocardial infarction (6) and stroke (7). In part, the susceptibility to vascular disease reflects the high prevalence of hypertension and dyslipidemia, as well as alterations in adipokines, leading to vascular inflammation in insulin-resistant patients (14, 15). However, more specific abnormalities in endothelial cell insulin signaling might also confer a direct susceptibility to vascular disease development and progression. Endothelial cell-specific insulin receptor knockout mice have reduced endothelial nitric oxide synthase expression, although they have normal vascular development and do not develop hypertension (16).

Insulin resistance is also common in patients with heart failure (17), raising the possibility that the systemic consequences of insulin resistance and/or specific impairment in myocardial insulin signaling might contribute to cardiac dysfunction. Obese insulin-resistant rodents (5) and mice with specific deletion of the cardiac insulin receptor (3, 4) have provided support for this hypothesis. Obese insulin-resistant rodents demonstrate cardiac lipid accumulation, left ventricular contractile dysfunction, and defective activation of the insulin receptor-phosphatidylinositol 3-kinase (PI 3-kinase)-protein kinase B (Akt) signaling pathway (5). Teasing apart the direct effects of altered hormones and substrates on the heart vs. their indirect effects attributable to alterations in cardiac insulin receptor signaling is difficult in these models. However, the specific absence of the cardiac insulin receptor in mice is also associated with oxidative stress, mitochondrial uncoupling, defective energy production, and minor contractile dysfunction (4). How these findings relate to humans is uncertain but of interest because obesity is associated with heart failure in epidemiological studies (8) and inefficient cardiac energy metabolism in imaging studies (13).

Human disease is arguably best studied in large animal models, which more closely replicate human physiology and therefore provide unique platforms for translational research. The recent investigation by Lee et al. (9) in this issue of the journal is an excellent example of such research and provides novel insights into the molecular mechanisms responsible for impaired cardiac insulin signaling in the diet-induced porcine model of obesity. The investigators documented blunted insulin-stimulated heart glucose uptake and PI 3-kinase activation following 7 mo of a high-fat diet that led to body weights 82% greater than in control animals. The impairment in myocardial glucose uptake was evident at the higher of two selected insulin infusion rates administered in the study. Insulin-resistant animals also had less reduction in arterial free fatty acid concentrations and heart fatty acid uptake during insulin infusion, a confounding factor that might have contributed to reduced heart glucose uptake via Randle cycle mechanisms. However, obese swine showed marked myocardial insulin resistance with respect to cell signaling with no evident stimulation of either insulin receptor substrate-1 (IRS-1)-associated PI 3-kinase activity or downstream Akt1 activation. This profound acquired cardiac insulin resistance mimics that seen in the cardi specific insulin receptor knockout mouse (3, 4) where genetic absence of the receptor similarly blocks effective insulin signaling. The porcine findings are of interest because the model replicated many of the features of human insulin resistance, namely, hyperinsulinemia, relative hyperglycemia, impaired skeletal muscle insulin signaling, hypertriglyceridemia, hypertension, and low plasma adiponectin levels (9).

Furthermore, the report by Lee et al. (9) provides insight into two distinct mechanisms potentially responsible for myocardial insulin resistance in diet-induced obesity. Hearts from obese animals demonstrated increased phosphorylation of the IRS-1 at Ser307, a residue located near the phosphotyrosine-binding domain that mediates the interaction of IRS-1 with the insulin receptor (2). Phosphorylation of Ser307 by kinases such as c-Jun NH2-terminal kinase (JNK) and S6 kinase-1 blocks activation of IRS-1 by the insulin receptor (2, 15). The authors also observed increased expression of the regulatory p85α subunit of PI 3-kinase in hearts from the obese compared with normal swine (9). During insulin stimulation, the insulin receptor phosphorylates IRS-1 tyrosine sites, which normally promotes IRS-1 binding to SH2 domains in the p85 subunit and subsequent activation of PI 3-kinase (15). PI 3-kinase is a heterodimetric protein containing both the regulatory p85α subunit and a catalytic p110 subunit. The authors observed an increased amount of p85α associated with IRS-1 at baseline but impaired recruitment of p85α and p110 catalytic subunit to IRS-1 following insulin stimulation (9). They postulate that monomeric p85α subunits bound to IRS-1 blocked the association of p85α-p110 heterodimeric complexes, resulting in the impairment in PI 3-kinase and Akt signaling observed (9). These findings build on prior work demonstrating that altered stoichiometry in the expression of p85α, p110, and IRS-1 alters the activation of PI 3-kinase in skeletal muscle (10).

The observations by Lee et al. (9) are of interest and raise several additional questions with regard to perturbations in insulin signaling and cardiac physiological function in diet-induced obesity. The authors provide evidence that excess IRS-1 serine phosphorylation occurs in insulin-resistant hearts,
but IRS-1 has >70 potential serine/threonine phosphorylation sites and the relative importance of these sites remains incompletely understood. Thus a logical question is how critical is the Ser\textsuperscript{307} site? In this regard, recent studies have shown that mice with Ser → Ala mutations in Ser\textsuperscript{302}, Ser\textsuperscript{307}, and Ser\textsuperscript{612} are protected against fat-induced insulin resistance in skeletal muscle (11). The Ser\textsuperscript{302} and Ser\textsuperscript{307} sites mediate interaction with phosphotyrosine domains on the insulin receptor, whereas the Ser\textsuperscript{612} site is one of several additional sites that modulate the interaction of IRS-1 with the p85 domain of PI 3-kinase (12).

Although the work by Lee et al. does not evaluate the phosphorylation status of other serine sites, increased baseline association of p85α with IRS-1 in the obese swine suggests that the primary consequence of increased IRS-1 phosphorylation is an alteration in transducing the insulin receptor response rather than prevention of PI 3-kinase binding. The study also raises the question as to which kinase(s) are responsible for the increased IRS-1 Ser\textsuperscript{307} phosphorylation in the obese porcine model. In rodent skeletal muscle, IRS-1 is phosphorylated by JNK and S6 kinase-1, the former activated by transforming growth factor-β and the latter by mammalian target of rapamycin and various growth factors, including insulin (1, 2). The upstream mechanisms leading to increased Ser\textsuperscript{307} phosphorylation thus need to be defined in this model.

The study by Lee et al. also raises important questions about the physiological implications of defective cardiac insulin signaling in obesity. Impaired insulin signaling in mouse models leads to a spectrum of abnormalities in left ventricle function, some relatively modest (3, 4), others more pronounced particularly under high workload conditions (5). In contrast, the obese porcine model demonstrated no impairment in hemodynamic indexes of left ventricular systolic or diastolic performance after 7 mo of dietary intervention (9). Despite the development of insulin resistance, hypertension, and cardiac lipid accumulation, the swine did not develop functional cardiac contractile abnormalities (9). The substantial early metabolic alterations without apparent physiological functional perturbations in the large animal model might well reflect what happens in diet-induced obesity in humans. Although the authors are to be commended on completing a demanding 7-mo study, is it possible that more long-term studies will be required to determine the relationship between diet-induced obesity, cardiac contractile abnormalities, and possible heart failure?

Obesity is a rapidly growing public health problem, and our understanding of how it impacts cardiac function is still in its infancy. Likely, heart failure related to obesity will be a complex clinical phenotype that is influenced by primary metabolic changes in the context of systemic hypertension, a proinflammatory state, and in many cases confounding coronary artery disease. The work by Lee et al. is an important step toward understanding the pathophysiology of insulin resistance in a clinically relevant large animal model, which should inspire and guide obesity research in the future.

REFERENCES


