Heart Smart Insulin-Like Growth Factor 1

Susan A. Marsh, Amy J. Davidoff

The prevalence of obesity, metabolic syndrome, and type 2 diabetes mellitus, and the associated cardiac pathologies are rising to alarming levels. Conventional medical therapies for the prevention and treatment of cardiomyopathy are less effective in patients with these metabolic disorders, and this is attributed, at least in part, to a limited understanding of the cellular and genetic mechanisms responsible for the pathology in the heart. The cause(s) underlying the development of obesity and metabolic syndrome have been attributed to several factors including, but not limited to, consumption of a high-fat diet and are often associated with myocardial contractile and metabolic dysfunction.1 The detrimental effects of high-fat diets on the heart are likely to be multifactorial and include lipotoxicity, abnormal fatty acid metabolism, endothelial dysfunction, impaired calcium handling, mitochondrial dysfunction, and disruption of the insulin signaling pathway. Recent evidence also suggests that a high-fat diet induces epigenetic defects in the heart,2 which could potentially result in an increased risk of cardiac pathologies in offspring. A better understanding of the mechanisms underlying the increased propensity for high-fat diets to induce cardiac dysfunction is necessary to develop treatment strategies.

Insulin-like growth factor-1 (IGF-1) plays a role in regulating cell proliferation, differentiation, survival, and metabolism and is produced in many tissues, including the heart. Reduced IGF-1 levels are associated with obesity, cardiovascular disease, atherosclerosis, and diabetes mellitus, whereas elevated IGF-1 has been associated with longevity in humans.3 A potential connection between IGF-1 and the effects of high-fat diets has only recently been reported in a study using the IGF-1 deficient Lewis dwarf rat and showed that endothelial dysfunction in this model is exacerbated by consumption of a high-fat diet.4 In the present issue of Hypertension, Zhang et al5 demonstrate a beneficial role for cardiac overexpression of IGF-1 in attenuating or preventing the contractile and metabolic dysfunction induced by high-fat feeding. These findings are consistent with previous work by the same group using a type 1 diabetic mouse model,6 showing that the IGF-1 deficiency observed in conditions such as obesity and diabetes mellitus contributes to abnormal cell signaling and metabolism in heart and that enhancing IGF-1 levels can prevent and perhaps reverse these pathologies (as seen in the high-fat diet group, Figures S4 and S5 in Reference 5).

Although there are distinct IGF-1 receptors, there is considerable cross-talk between insulin and IGF-1 actions, and, similar to the insulin receptor, the IGF-1 receptor belongs to a tyrosine kinase receptor superfamily, which undergoes autophosphorylation on ligand binding. Downstream of these receptors are 2 major pathways, mitogen-activated protein kinase/extracellularly regulated kinase and phosphoinositol 3-kinase, which play major roles in cell survival, cellular metabolism, and transcriptional regulation of cell growth. Therefore, it is not entirely surprising that restoration of IGF-1 levels in hearts of high-fat fed animals also prevented abnormalities in cardiac function and metabolism. It is interesting to note that, whereas high-fat diet–induced cardiac dysfunction was alleviated by IGF-1 overexpression, cardiomyocyte hypertrophy was not altered. In cardiac tissue, IGF-1 is associated with physiological hypertrophy through the IGF-1 receptor–phosphoinositol 3-kinase (p110α)–Akt pathway.7,8 Perhaps the hypertrophy in the IGF-1 groups, indicated by cell size in Figure 4 of Reference 5 may represent a physiological hypertrophy that would be consistent with the contractile data. Further assessment of markers for pathophysiological hypertrophy is necessary to make such distinctions.

The results of the IGF-1 cardiac-specific transgene used in these investigations are somewhat complicated by the observations that plasma levels of IGF-1 are elevated, as well as cardiac IGF-1 levels (Table 1 in Reference 5). However, similar cardioprotection from type 1 diabetes mellitus has been shown in mice overexpressing IGF-1 receptors,9 thereby supporting the notion that cardiac-specific IGF-1 signaling plays a role, rather than an effect solely due to increased systemic IGF-1 levels. It should be emphasized that overexpression of cardiac IGF-1 did not alter peripheral glucose metabolism or inflammatory markers, confirming that the beneficial effects were unlikely to be the result of normalized systemic metabolism. Collectively, these observations are intriguing in that upregulation of cardiac IGF-1 may be sufficient to block the detrimental cardiac effects of a high-fat diet and have potentially profound implications for our understanding of metabolic dysregulation in the heart. The authors present a scheme to highlight their findings (Figure S6 in Reference 5) and propose that high-fat feeding reduces cardiomyocyte IGF-1 signaling, which, in turn, leads to mitochondrial dysfunction, intracellular Ca2+ dysregulation,
and abnormal insulin signaling. Although plausible, the order of these events has not been confirmed.

The markedly beneficial effect of IGF-1 overexpression in the heart also raises the question as to whether pharmacological therapies designed to increase IGF-1 levels in the clinical setting will be effective in reducing the incidence, or possibly the severity, of high-fat diet–induced cardiac pathology. In a recent article, Troncoso et al reported that short-term treatment with IGF-1 was cardioprotective against nutrient-deprived stress; IGF-1 prevented cardiomyocyte stress-induced autophagy in cells and animals by increasing ATP levels and mitochondrial metabolism, including mitochondrial Ca²⁺ levels and oxygen consumption, through the Akt/mammalian target of rapamycin axis. It is important to note that the cardioprotective effects against autophagy are similar to those mechanisms shown to be protective in animals overexpressing cardiac-specific IGF-1 and fed a high-fat diet. Thus, the mechanisms underlying IGF-1 protection are likely to be multifactorial and include several different but related signal transduction pathways.

Despite early clinical trials showing great promise of IGF-1 for the treatment of diabetes mellitus related to glucose control, mescalain (Increlex), an IGF-1 analog, is currently the only US Food and Drug Administration approved drug available and is only approved for treatment of IGF-1 deficiency. There is concern that chronic systemic IGF-1 can increase retinopathy, induce fibroblast proliferation, and increase risk of cancer in a variety of tissues. Thus, while short-term IGF-1 therapies may afford positive effects, chronic use may result in adverse effects, severely diminishing their clinical use. Several investigators have used the strategy of overexpressing cardiac–specific IGF-1 or IGF-1 receptor, and this approach appears to yield strikingly beneficial results, while avoiding unwanted systemic effects of chronically elevated IGF-1 levels.

In conclusion, although it is clear that reduced IGF-1 signaling is involved in either initiating or propagating the detrimental effects of a high-fat diet on cardiac function, it is somewhat premature to suggest that IGF-1 is the sole mediator of this process because of the complex nature of fat metabolism and downstream signaling pathways. Nevertheless, the development of cardiomyocyte-specific IGF-1 therapies may help to alleviate the incidence of cardiomyopathies induced by high-fat diets (as well as by diabetes mellitus), while avoiding the systemic complications caused by current IGF-1 pharmacotherapies. This approach also raises the issue as to whether drug or gene therapies should be designed and implemented to attenuate or reverse pathologies that are induced by lifestyle choices, such as consumption of a high-fat diet. Because of the high rate of recidivism after lifestyle modification therapies, alternative therapies are clearly warranted.

Sources of Funding

S.A.M. is supported by National Institutes of Health grant HL-104549 and the Washington State University College of Pharmacy.

Disclosures

None.

References
