U nder physiological circumstances, insulin regulates substrate utilization in multiple tissues, including the heart, skeletal muscle, liver, and adipose tissue. In the heart, insulin stimulates glucose uptake and oxidation and although it increases fatty acid (FA) uptake, it inhibits FA utilization for energy. Generalized insulin resistance occurs primarily as a result of obesity, a consequence of caloric excess, physical inactivity, genetics, and age. Insulin resistance is associated with many serious medical conditions such as type 2 diabetes mellitus, hypertension, atherosclerosis, and metabolic syndrome. In diabetes mellitus and insulin-resistant states, metabolic, structural, and functional changes in the heart and vasculature led to diabetic cardiomyopathy, coronary artery disease, myocardial ischemia, and ultimately heart failure. There are many molecular mechanisms that contribute to the association between insulin resistance and increased cardiovascular disease. These include the impact of insulin resistance to induce impaired vascular function, which leads to impaired nitric oxide–mediated vasorelaxation, which may contribute to hypertension and increased risk of atherosclerosis. Moreover, genetic manipulation of insulin action in the vasculature will increase atherosclerosis. Insulin resistance via multiple mechanisms may contribute to macrophage accumulation in the vessel wall to increase atherosclerosis and instability of vulnerable plaques. Finally, insulin resistance has been shown in many human and animal studies to increase the extent of myocardial injury in the context of myocardial ischemia, which may contribute to the increased risk of heart failure in affected individuals. The interactions between insulin resistance and vascular disease will be the subject of other reviews in this series. The present review will focus on the mechanisms by which insulin resistance develops and contributes to structural heart disease. Although incompletely understood, these mechanisms involve the combination of changes in insulin signaling transduction pathways in the heart acting in concert with changes in mitochondrial function and metabolism glucose and free fatty acids (FFAs).

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Insulin Signaling in the Heart and the Molecular Changes in Insulin Resistance

Insulin release from pancreatic β-cells induces glucose uptake in cardiomyocytes, skeletal muscle, and adipose tissue on binding of insulin to the cell surface insulin receptor (IR). The IR undergoes autophosphorylation after insulin binding, which initiates a signaling cascade initiated by tyrosine phosphorylation of IR substrates, followed by phosphorylation of phosphatidylinositol 3-kinase, phosphoinositide-dependent kinase-1, Akt, and protein kinase C. These events result in glucose transporter type 1 and type 4 (GLUT1 and GLUT4) translocation to the membrane to facilitate glucose uptake in the cell. Although insulin-mediated translocation of GLUT4 is a major regulator of glucose utilization in glycolytic and oxidative skeletal muscle, in the heart it is likely that contractile-mediated translocation of GLUT4 represents the major mechanism that regulates glucose entry in the beating heart, with GLUT1 playing a lesser role. Thus, insulin stimulation in isolated working hearts or in vivo increases myocardial glucose utilization by 40% to 60%, in contrast with a 3- to 8-fold increase in insulin-treated skeletal muscle in vivo or in vitro.

In addition to glucose uptake, insulin-mediated activation of phosphatidylinositol 3-kinase and Akt regulates many other cellular processes such as cellular hypertrophy, protein translation, nitric oxide generation, apoptosis, and autophagy by activating other intracellular signaling intermediates such as mammalian target of rapamycin, S6K, and forkhead transcription factors (eg, FOXO1/3, glycogen synthase kinase-3β, and nitric oxide synthase III). Changes in many of these signaling pathways as developed in insulin-resistant states could contribute to an increased risk of cardiac hypertrophy, adverse left ventricular (LV) remodeling, or heart failure.

In discussing the concept of myocardial insulin resistance, it is important to distinguish between effects that are secondary to the disturbed systemic milieu in insulin-resistant states (hyperinsulinemia, hyperglycemia, and hyperlipidemia) and changes that occur in insulin signaling pathways that are intrinsic to the cardiac tissue. The earliest and most consistent change that develops in the hearts in animal models in the evolution of insulin resistance is impairment in the ability of insulin to increase glucose transport. This early change occurs before any defect in the ability of insulin to increase phosphatidylinositol 3-kinase and Akt signaling and occurs as a consequence of both reduced GLUT4 protein and impaired GLUT4 translocation. Similar changes have been reported in ventricular muscle biopsies obtained from subjects with type 2 diabetes mellitus. Indeed in this human study, diabetes mellitus was associated with increased signaling to Akt and phosphatidylinositol 3-kinase, despite reduced GLUT4 translocation to the plasma membrane. A recent study in mice also revealed that the generalized insulin resistance and hyperinsulinemia that develops in the context of pressure overload cardiac hypertrophy drives excessive myocardial insulin signaling to Akt that contributes to accelerated LV remodeling and the transition to heart failure. In support of this concept, decreased myocardial insulin signaling may represent a mechanism for the potential benefit of high-fat diets in ameliorating heart failure in rodent models of pressure overload or post-myocardial infarction LV remodeling. Thus, in considering the impact of insulin resistance on the heart, it is important to distinguish between the effects that are secondary to hyperactivation of signaling pathways that may remain responsive to insulin versus changes that are the consequence of an impaired ability of insulin to modulate glucose metabolism. In animal models with long-term exposure to high-fat diets or in genetic models of severe insulin resistance such as ob/ob and db/db mice, clear evidence exists for an impaired ability of insulin to activate intracellular signaling kinases, such as Akt or FOXO1, which might also contribute to LV dysfunction. Indeed, genetic inactivation of insulin signaling in the heart has been shown to contribute to LV dysfunction by increasing mitochondrial dysfunction, decreasing angiogenesis, and increasing fibrosis particularly in response to hemodynamic stressors. Thus, given the broad spectrum of abnormalities that may characterize cardiac insulin resistance, it is critical to dissect and distinguish between those mechanisms that are a consequence of increased or decreased signal transduction to intracellular kinases, changes that are secondary to intrinsic regulation of substrate metabolism, or changes that are secondary to altered delivery of substrates to the heart.

Because of its high and tightly regulated energy demands, changes in systemic insulin sensitivity or changes in myocardial insulin action can significantly impact cardiac metabolism and function. The constant demand for mechanical power in the heart is met by high rates of ATP production from fat and carbohydrate oxidation. The myocardium rapidly adjusts to fluctuations in circulating substrate concentrations, giving the heart the metabolic flexibility needed for feeding, fasting, and intense exercise. Insulin resistance impairs the ability of the heart to adjust to changing energy demands by increasing the delivery of FAs to the heart and by reducing the ability of the heart to use glucose, thereby shifting the heart toward a greater reliance on FAs for energy. As a result, the diabetic heart undergoes cellular stress, including elevated reactive oxygen species (ROS) production, mitochondrial dysfunction, and apoptosis. These changes in myocardial metabolism that occur as a result of insulin resistance may contribute to downstream structural and functional alterations in the heart that can lead to cardiomyopathy and heart failure. Although there are many aspects of insulin resistance that impact the heart, this review will focus on the mechanisms of insulin resistance in the heart related to glucose and FA metabolism.

Glucose and FA Metabolism in the Heart

Upon insulin-mediated uptake of glucose into the cell, glucose is converted to glucose-6-phosphate by hexokinase in heart, skeletal muscle, and adipose tissue. Glucose-6-phosphate has several fates in the cell, but the 2 primary fates are glycogen for energy production and glycogen for storage, both of which are augmented by insulin signaling. Under ambient physiological conditions, a small percentage of glucose is shunted to the hexosamine biosynthesis pathway, pentose phosphate pathway, or the polyol pathway and glycolysis and subsequent glucose oxidation accounts for ≈20% of total myocardial energy generation. Short-term hyperglycemia can increase total myocardial glucose utilization to 60% to 70% of total energy generation. However, in the context of
diabetes mellitus, these changes are not long lasting because of downregulation of glucose transport and increased delivery of FAs to the heart.\(^9\)

Circulating FFAs contribute to the development of insulin resistance via several mechanisms. Circulating concentrations of plasma FFAs are determined to a large extent by the adipose triglyceride lipase and hormone-sensitive lipase–stimulated release of adipocyte triglyceride stores.\(^{40}\) Hormone-sensitive lipase–stimulated release of FFAs from triglyceride stores in adipose tissue is tightly controlled by hormones that are regulated by the metabolic status.\(^33\) During conditions such as fasting, when blood glucose is low or when energy demands are increased, glucagon, glucocorticoids, and catecholamines lead to activation of hormone-sensitive lipase to promote hydrolysis of triglycerides to FFAs. By contrast, in the fed state, insulin inactivates hormone-sensitive lipase and inhibits lipolysis.\(^33\) In vivo, most FFAs that are delivered to tissues arise from hydrolysis of a triglyceride, which are transported in plasma in chylomicrons or very low-density lipoprotein particles and the remainder exist in the nonesterified form bound to albumin. Plasma FFAs can increase in healthy individuals due to adrenergic stimulation brought on by exercise, stress, fasting, ischemia, or diabetes mellitus. The release of FFAs from chylomicrons or very low-density lipoproteins by lipoprotein lipases in these situations also increases plasma FFAs.\(^33\)

After FAs are taken up by target tissues, they have 3 major fates in the cell. They can be esterified into triglycerides, diglycerides, or phospholipids; converted to sphingolipids; or oxidized for energy.\(^41\) FFAs are transported across the sarcolema and into the cardiomyocyte by either passive diffusion or transport proteins (FA translocase or FA-binding proteins).\(^33\) Because most FFAs that enter the heart are used for energy (70–90%),\(^42\) they must enter the mitochondrial matrix for \(\beta\)-oxidation. FFAs are transported across the outer and inner mitochondrial membrane by carnitine palmitoyltransferase 1, which is the rate-limiting step of FA oxidation and carnitine palmitoyltransferase 2. The acetyl-CoA resulting from \(\beta\)-oxidation enters the tricarboxylic acid cycle, yielding NADH and FADH\(_2\), which enter the electron transport chain to produce ATP.\(^33\) Persistent exposure of tissues to increased concentrations of FAs and associated changes in the metabolic fate of FAs are important causes of insulin resistance.

**Obesity, Lipotoxicity, and Insulin Resistance**

Obesity is the leading cause of insulin resistance, and obese individuals tend to have higher plasma FFAs as a result of decreased suppression of lipolysis by insulin resistance. It is also believed that an impaired ability of adipocytes to store excess calories as triglycerides also contributes to increased accumulation of lipids and their metabolites in other tissues that are not necessarily adapted to lipid storage such as muscle and liver. As a result, the accumulation of lipid metabolic intermediates incites a variety of cellular abnormalities such as apoptosis, oxidative stress, and endoplasmic reticulum stress, which impairs cellular function.

FFAs are the main substrate for ATP production in the heart under normal conditions. FFAs undergo \(\beta\)-oxidation to yield 60% to 70% of the energy needed to maintain cardiac work.\(^37\) The level of circulating FFAs largely determines FFA uptake in the heart.\(^33,42,43\) In situations where FFAs are elevated, myocardial lipid accumulation can occur, which is detrimental to LV function. Myocardial lipid accumulation occurs as a result of a mismatch between FA uptake and oxidative metabolism, which increases the partitioning of lipids into other metabolic pathways that may contribute to impaired insulin action in the heart such as reduced insulin-stimulated glucose transport and impaired insulin signaling.\(^1\) Increased availability and utilization of FFAs led to the accretion of triglycerides and lipid metabolites, such as long-chain acyl-CoAs and diacylglycerol in the heart and other tissues, including liver and skeletal muscle.\(^44\) Although triglyceride accumulation is often interpreted as a cause of lipotoxicity, it is likely that the triglycerides per se might not represent the toxic lipid moiety but may represent a mechanism by which the tissue is attempting to sequester the excess lipids into a relatively inert pool.\(^45\) However, lipid metabolites, such as diacylglycerol, stimulates protein kinase C-\(\Phi\), which is a serine/threonine kinase that may inhibit insulin signaling by increasing the serine phosphorylation of IR substrate proteins.\(^7,48\) In mice fed a high-fat diet for 10 weeks, cardiac insulin resistance as evidenced by a decrease in glucose oxidation was associated with an increase in diacylglycerol, but not triacylglycerol, ceramide, or long-chain acyl-CoA,\(^49\) suggesting that diacylglycerol accumulation may play a role in high-fat diet–induced insulin resistance in the heart.

Lipid-induced cardiac dysfunction (cardiac lipotoxicity) may contribute to apoptosis,\(^50\) impaired mitochondrial function,\(^51\) and ultimately to cardiac dysfunction. The heart has a limited capacity to store triglycerides, thereby increasing its susceptibility to the consequence of accumulation of toxic lipid species.\(^52\) An underappreciated mechanism that may contribute to lipotoxicity in the insulin-resistant state is hyperinsulinemia itself. As discussed earlier, the ability of insulin to activate Akt may be relatively preserved in the heart. Akt activation promotes the translocation of CD36 to the plasma membrane, which would increase the uptake of FAs.\(^53\) However, the concurrent inhibition of mitochondrial FA oxidation increases the flux of FAs into lipid storage pathways, thereby contributing to lipotoxicity. Transcription factors related to lipid metabolism have also been implicated in the pathogenesis of lipotoxicity. Peroxisome proliferator–activated receptors (PPARs), which are members of the nuclear receptor superfamily of transcription factors, are key regulators of FA metabolism.\(^54\) There are 3 major PPAR isoforms: PPAR\(\alpha\), PPAR\(\beta/\delta\), and PPAR\(\gamma\), which have distinct but overlapping functions in regulating FA metabolism and are differentially expressed in various tissues. Transgenic mice overexpressing cardiac-specific PPAR\(\gamma\) display augmented expression of FA oxidation genes, dilated cardiomyopathy, and enhanced lipid deposition in the heart.\(^55\) Cardiac-specific overexpression of PPAR\(\alpha\) in mice leads to enhanced \(\beta\)-oxidation of FAs and reduced glucose oxidation and accumulation of triglycerides.\(^56\) Myocardial insulin
resistance may also contribute to contractile dysfunction in these hearts.77 Conversely, PPARα-null mice have reduced rates of β-oxidation of FAs, elevated rates of glucose oxidation, cardiac fibrosis, and they cannot maintain cardiac output during conditions of increased workload.58,59

Another transcription factor involved in lipotoxicity is sterol regulatory element–binding protein-1c, which regulates hepatic lipogenesis and converts glucose to FAs and triglycerides during conditions of overnutrition.60,61 Sterol regulatory element–binding protein-1c is activated by insulin during insulin resistance.62 Furthermore, there is a correlation between reduced ejection fraction and lipid accumulation within cardiomyocytes of patients with the metabolic syndrome and increased levels of sterol regulatory element–binding protein-1c and PPARγ in the heart.63 This suggests that sterol regulatory element–binding protein-1c can promote lipid deposition in cardiomyocytes in the metabolic syndrome by upregulating PPARγ, which promotes lipotoxicity and contractile dysfunction.

Ceramide is a sphingolipid that is a key mediator of cellular stress pathways that induce apoptosis and mitochondrial dysfunction. In normal physiology, ceramide is derived from de novo synthesis or can be derived from sphingomyelin hydrolysis. Ceramide acts as a lipotoxic intermediate when it builds up as a result of elevated circulating FFAs. The role of ceramide in insulin resistance in skeletal muscle has been studied more closely than in the heart. Ceramide and ceramide metabolites interfere with insulin signaling by activating protein kinase C-ζ,64 blocking Akt activation and subsequently reducing glucose uptake.65 In skeletal muscle, ceramide decreases GLUT4 translocation to the membrane66,67 and inhibition of serine palmitoyltransferase 1 reverses insulin resistance.68 We recently showed that ceramide also plays an important role in the pathogenesis of obesity-mediated vascular dysfunction via a mechanism that involves protein phosphatase 2A–mediated dephosphorylation of nitric oxide synthase III.5 Moreover, the treatment of mice with lipotoxic cardiomyopathy with the inhibitor of ceramide synthesis myriocin reversed contractile dysfunction in a mouse model of lipotoxic cardiomyopathy.69 Taken together, it is therefore likely that ceramide accumulation may contribute to the pathogenesis of cardiac dysfunction in insulin-resistant states.

**Other Mediators of the Interaction of Insulin Resistance and Cardiac Dysfunction**

Recent studies have implicated novel mechanisms that may directly contribute to the pathophysiology of insulin resistance and its cardiovascular complications,64 such as changes in AMP-activated protein kinase (AMPK) signaling,70 oxidative stress,71 inflammation,72 advanced glycation end products (AGEs),73 endoplasmic reticulum stress,74 autophagy,75 and changes in adipokines.76 Some of these mechanisms are discussed in more detail below.

**AMP-Activated Protein Kinase**

AMPK is an important mediator of energy balance in various tissues, including the heart.77 Under conditions of inhibited ATP production or elevated ATP consumption, such as ischemia or exercise, the AMP:ATP ratio is elevated and AMPK is stimulated. As a result, AMPK acts to maintain ATP production and contractile function by increasing glucose and FA uptake and oxidation in the heart.78–80 AMPK directly impacts FA metabolism through the inhibition of acetyl-CoA carboxylase, which is responsible for the synthesis of malonyl CoA, a potent inhibitor of carnitine palmitoyltransferase 1. AMPK directly enhances insulin signaling in endothelial cells, protecting from insulin resistance.81 It is possible that obesity-related impairment of AMPK function may contribute to insulin resistance in the heart. Moreover, a reduced circulating level of adiponectin, which is a characteristic of obesity, is associated with impaired AMPK signaling and mitochondrial biogenesis.82 These observations raise the possibility that reduced activity of AMPK might contribute to mitochondrial dysfunction in the heart in obesity and insulin-resistant states.

**Reactive Oxygen Species and Insulin Resistance**

Obesity is associated with increased oxidative stress in the heart and vasculature.14 The sources of ROS are mitochondrial and extramitochondrial. For example, hyperglycemia may contribute to ROS production by activation of NADPH oxidase in cardiomyocytes.83 Ceramide may also contribute to ROS by reducing the mitochondrial ubiquinone pool of complex III84,85 and increasing NADPH oxidase activity in endothelial cells.86 Although the mitochondria are largely responsible for generating ROS, they can also be damaged by ROS. Oxidative stress has also been implicated in the pathophysiology of insulin resistance both in animals and in cultured cells.48 It is not yet known if oxidative stress will impair myocardial insulin action. However, there is strong evidence that oxidative stress may contribute to mitochondrial dysfunction in obesity and insulin-resistant states.87 ROS in the heart can act as a second messenger, initiating hypertrophic signaling, extracellular matrix remodeling, and apoptosis.88

**Inflammation and Insulin Resistance**

It is generally accepted that systemic inflammation contributes to insulin resistance.89 Proinflammatory cytokines induce insulin resistance, which may influence the fate of glucose and FA utilization via direct and indirect mechanisms. By inducing insulin resistance, inflammation will increase the reliance of the heart on triglycerides from the liver and FFAs from adipose tissue for energy.90 Obesity is accompanied by an increase in circulating concentrations of inflammatory cytokines, such as interleukin-6 and tumor necrosis factor-α. These are believed to be derived in large part from macrophage infiltration of adipose tissue.90 Given the well-documented associations among inflammation, obesity, and insulin resistance in other tissues,91 inflammation in the heart may be a contributor to myocardial insulin
resistance. Inflammatory cytokines impair insulin signaling by activating intracellular signaling kinases such as Jun N-terminal kinase that impairs insulin signaling by increasing the serine phosphorylation of IR substrate proteins. It is possible that this mechanism may potentially occur in cardiomyocytes. Ko et al reported that high-fat feeding increased inflammation in the obese mouse heart, as evidenced by interleukin-6–mediated increases in macrophage and cytokine infiltration into the heart. In addition, glucose oxidation was reduced as a result of cardiac inflammation in an interleukin-6–dependent manner. It remains to be demonstrated if the local increase in myocardial inflammation directly contributes to impaired myocardial insulin action or if the metabolic changes are secondary to systemic changes.

**AGEs and Insulin Resistance**

Several studies have reported interesting associations between AGE levels and insulin resistance, even in the absence of diabetes mellitus. Studies by Tan et al in healthy nondiabetic subjects showed an association among AGE levels, inflammatory markers, and insulin resistance (the latter by the homeostatic model assessment index or homeostatic model assessment index-IR). Tahara et al reported correlation between serum AGE levels and homeostatic model assessment index-IR in Japanese subjects. Sarkar et al found a highly significant correlation between the degree of insulin resistance and pre-AGE carbonyl levels in subjects with type 2 diabetes mellitus. Recent animal studies demonstrated that flux via the aldose reductase (AR) pathway in hyperglycemia contributes to driving formation of pre-AGE methylglyoxal and oxidative stress. In an AGE-enriched environment of aging, treatment with AR inhibitors reduces levels of methylglyoxal and AGEs. Interaction of AGEs with its receptor RAGE has been linked to poor outcome after ischemic stress in diabetic and nondiabetic hearts. AGE precursor generating AR pathway has also been demonstrated to play a key role in mediating ischemic injury and cardiovascular complications in diabetes mellitus. These data suggest that examination of AR and RAGE is likely to be useful in determining potential relationships to impaired myocardial insulin action.

**Therapeutic Implications**

Therapies that modulate generalized insulin resistance such as PPARα or PPARδ agonists have been shown in animal models to improve myocardial function in part by decreasing circulating levels of FAs and switching myocardial substrate metabolism toward glucose. However, thiazolidinediones also induce cardiac hypertrophy via mechanisms that might be independent of effects on myocardial insulin signaling, which might independently contribute to increased heart failure risk. Moreover, recent analyses of this therapeutic class in humans have indicated an independent increase in cardiovascular mortality resulting from increased coronary events. Fewer studies have directly examined the impact of insulin sensitizers on cardiac structure, function, and metabolism in humans with diabetes mellitus. In a study of well-controlled subjects with type 2 diabetes mellitus, pioglitazone modestly improved diastolic dysfunction in association with increased glucose utilization, whereas metformin treatment was without effect. Metformin on the other hand may have a potentially beneficial impact on cardiovascular outcomes via mechanisms that might not only be related to its impact to improve systemic metabolic homeostasis but via mechanisms that may include beneficial impact of increasing AMPK signaling and the repression of autophagy. The notion that excessive insulin signaling and hyperinsulinemia may accelerate LV remodeling on the basis of hyperactivation of Akt raises a therapeutic conundrum, in that 1 consequence of achieving metabolic control in subjects with type 2 diabetes mellitus is the use of increased doses of insulin that will increase hyperinsulinemia and increase Akt signaling in the heart. Indeed, analyses of the impact of tight metabolic control on the outcomes on cardiovascular outcomes or heart failure have been disappointingly neutral or, in the case of heart failure, could potentially worsen heart failure risk. Thus, it is imperative to explore the impact of novel therapeutic strategies for treating diabetes mellitus such as agents that modulate GLP1 signaling on the interactions between insulin resistance and cardiac structure, metabolism, and function. Moreover, additional studies in humans are required to investigate the impact of therapies that modulate inflammation, endoplasmic reticulum stress, autophagy, and other novel mediators of insulin resistance on cardiovascular outcomes in insulin-resistant states.

**Concluding Remarks**

The mechanisms for and consequences of insulin resistance in the heart are complex and multifactorial. Whereas impaired insulin-stimulated glucose uptake is a common observation, changes in upstream signaling kinases are variable and may be increased or decreased, with varied impact on cardiac structure and function. The heart requires a constant, tightly regulated supply of energy, relying primarily on FA oxidation to meet this demand. Glucose oxidation also contributes to the energy demand of the heart; however, in insulin-resistant states the contribution of glucose is decreased, whereas that of FAs is proportionately increased. The main cause of insulin resistance is obesity and the associated increase in FFA delivery to the heart precipitates many problems in the cardiomyocyte, including lipotoxicity, ROS production, oxidative stress, and changes in insulin signaling. One unexplored territory in the field of cardiac insulin signaling is the role of AGEs, its receptor RAGE, and the pre-AGE generating AR pathway. The potential interplay between known metabolic mediators of insulin resistance and the unexplored pathways is summarized in the Figure. In conclusion, the development of new therapeutic targets that may normalize impaired myocardial insulin action may contribute to novel strategies for the treatment of diabetic heart disease.
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