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Insulin Signaling And Insulin Resistance

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Abstract

Insulin resistance or its sequelae may be the common etiology of maladies associated with metabolic syndrome (e.g., hypertension, type 2 diabetes, atherosclerosis, heart attack, stroke and kidney failure). It is thus important to understand those factors that affect insulin sensitivity. This review stems from the surprising discovery that interference with angiotensin signaling improves insulin sensitivity and it provides a general overview of insulin action and factors that control insulin sensitivity.

Introduction

“The most exciting phrase to hear in science, the one that heralds new discoveries, is not ‘Eureka!’ (I found it!) but ‘That’s funny ...’” Isaac Asimov

The American Federation for Medical Research sponsored a mini-symposium entitled “Angiotensin-Insulin Cross Talk—A True Translational Story from Bedside to Bench” at the 2011 annual meeting of the American Physiological Society. There were two “that’s funny” stories that led to the “Bedside to Bench” theme of this symposium. The first was a report that insulin resistance could be the main etiology underlying essential hypertension¹. The second story comes from a collection of observations indicating that interference with angiotensin signaling improves insulin sensitivity. Folli² and Prabhakar³ discussed these discoveries in more detail. The purpose of this article is to connect these two “that’s funny” events by providing an overview of insulin action and insulin resistance. Navar provides an overview of rennin/angiotensin signaling⁴ in this context.

Insulin Function And Physiology

Cheng *et al.* described the physiology of insulin action by saying: “The insulin signaling system coordinates systemic growth and development with peripheral and central nutrient homeostasis, fertility and lifespan”⁵. This simple statement underscores the importance of insulin action in a powerful way. Indeed, insulin regulates glucose uptake, glycogen synthesis, gluconeogenesis, lipid metabolism, hunger, cell growth and division, gene expression and protein synthesis, and vasodilatation⁵⁻⁷.

Consider for a moment the signaling symphony that occurs constantly within our bodies. Cells tissues and organs continually sense and integrate food availability, dietary composition, adiposity, cellular ATP and NADH, inflammation, and many other factors^{5,8}.

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At the systemic level, this requires neuroendocrine pathways involving the brain, gut, pancreas and adipose tissue⁹⁻¹¹. At the target tissue level, insulin signaling provides one of the major inputs responsible for fuel homeostasis, and a major output that integrates many of these input signals is the regulation of insulin sensitivity in target tissues. For example, elevated plasma fatty acids results in a physiological resistance to the action of insulin^{12,13}.

Insulin Signaling Pathways

The reader is referred to reviews and texts for details of insulin action e.g., see^{5,6,7}. Figure 1 presents a brief overview of the two known insulin-signaling pathways. These pathways are activated when insulin binds to the insulin receptor at the plasma membrane (note that IR-A and IR-B are splicing variants with slightly different properties and functions). Insulin interaction with its receptor activates an intrinsic tyrosine protein kinase, which autophosphorylates the receptor as well as downstream substrates. In the dominant pathway, a family of proteins known as Insulin Receptor Substrates (IRS) serves as the immediate downstream substrates, which activate a cascade of serine-protein kinases. Akt (protein kinase B) is a major branch point with numerous downstream substrates leading to a variety of physiological functions including the regulation of fuel homeostasis. The alternate pathway (“ras/MAP-kinase”) is also a serine-protein kinase cascade. However this pathway regulates transcription, cell growth and differentiation, and protein synthesis^{7,14}.

Crosstalk occurs at multiple levels in both of these signaling pathways as a result of signaling from other pathways. The focus of the symposium was crosstalk with the angiotensin-signaling pathway. The mechanisms of this cross talk are described by Folli² and Prabhakar³.

Metabolic Syndrome (Insulin Resistance Syndrome)

Reaven originally described metabolic syndrome¹⁵. It is clinically defined by having at least three of the following conditions: hypertension, elevated fasting blood sugar, obesity, low HDL cholesterol and elevated triglycerides^{16,17}. These conditions increase the risk of complications including atherosclerosis, type II diabetes, heart attack, kidney disease, fatty liver, vascular disease, stroke, and numerous other diseases^{16,17}. While the “typical” individual with metabolic syndrome has central obesity, individuals can be obese but metabolically lean, and lean but metabolically obese¹⁷. Another view of the metabolic syndrome is the presence of one or more of these complications in individuals who are insulin resistant. Though somewhat controversial, many have argued that the underlying etiology could be insulin resistance^{1,17,18}. This is not to imply that insulin resistance is directly responsible. Indeed, the chronic hyperinsulinemia that accompanies insulin resistance (prior to beta cell insufficiency) could be responsible for much of the pathology of metabolic syndrome through a constant “hyperactivation” of insulin and IGF-1 receptors.

Insulin Resistance

Pathological insulin resistance develops through complex interactions of genotype and lifestyle (lack of exercise and over-nutrition)¹⁹⁻²². It is important to recognize that insulin sensitivity in target tissues is regulated physiologically by circulating factors. These factors include plasma lipids, circulating hormones and adipokines, and their respective signaling pathways^{11,23,24}. Crosstalk among these various signaling pathways with the insulin signaling pathways constantly tunes insulin sensitivity. Adipose tissue, along with the brain and the gut, constitute a neuroendocrine axis that regulates metabolism in large measure by regulating insulin sensitivity in target tissues^{23,24}.

For example, the central role of adipose tissue is illustrated in Figure 2. Adipocytes serve a double duty of: 1) storing fat as triglyceride and releasing it as fatty acids and glycerol as needed; and 2) releasing a variety of hormones, collectively known as adipokines. Target tissues such as skeletal muscle can oxidize the fatty acids for fuel. In addition, elevated levels of circulating fatty acids can desensitize target tissues to the actions of insulin, as for example following a fatty meal.

Adipokine functions can be broken into two general categories—those that stimulate and those that inhibit insulin sensitivity. Leptin and adiponectin stimulate insulin action in peripheral tissues^{23,24}. Leptin is released from adipocytes in proportion to adiposity. In addition to its peripheral actions, it acts on the hypothalamus to suppress appetite. In contrast, adiponectin is released from adipocytes in inverse proportion to adiposity.

The adipokines that inhibit insulin sensitivity include TNF α , resistin, IL-6, and retinol binding protein 4, to name a few²³. These inhibitory factors are released by adipocytes in proportion to adiposity. Collectively, these adipocyte-derived factors regulate metabolism and feeding. However, lifestyle, obesity and genetics can collaborate to perturb this delicate balance²².

The perturbations caused by obesity are simplistically summarized as follows. Critical changes occur with two insulin-sensitizing factors—leptin levels rise and adiponectin levels fall in obese individuals. The hyperleptinemia leads to a paradoxical decrease in insulin sensitivity because it results in insensitivity to the action of leptin in its target tissues²³. Simultaneously there are changes in insulin-desensitizing factors—the levels of circulating fatty acids and inhibitory adipokines increase during obesity^{11,23}. Moreover, adipocytes secrete chemoattractant molecules that recruit macrophages such that the number of macrophages present in adipose tissue is increased in obesity²⁵. These macrophages also contribute to the concentration of circulating TNF α . The collective effect of all of these changes is increased appetite along with a pathological decrease in sensitivity to insulin in target tissues.

The central role of adipose tissue in the regulation of whole body insulin sensitivity is further illustrated by the following. 1) In most individuals obesity results in insulin resistance and can lead to insulin resistance syndrome. 2) In contrast, lipodystrophy also results in profound insulin resistance and metabolic syndrome²⁶. Superficially this is an apparent paradox in that too little body fat also leads to insulin resistance. The underlying reasons can be understood by referring to Figure 2. Briefly, the lack of adipose tissue results in leptin and adiponectin deficiencies along with inadequate stores for lipids. Circulating fatty acids and other lipids are increased for lack of adequate storage depots. These conditions collectively lead to insulin resistance. 3) The central role of leptin is dramatically underscored in the phenotype of individuals who either lack leptin or lack a normal leptin receptor due to mutations in the genes that encode these proteins. These individuals become profoundly obese and insulin resistant²⁷. 4) Finally, drugs of the thiazolidinedione class target PPAR γ in adipose tissue to improve insulin sensitivity in other tissues, an effect that has recently been shown to center on PPAR γ phosphorylation by cdk5 and normalization of adipocyte-derived factors (Figure 2)²⁸.

Despite this mass of information, much remains to be learned about the mechanisms that cause insulin resistance, and the mechanisms by which insulin resistance causes disease. During the past few years numerous genome wide association studies have been directed at identifying the genes that cause type II diabetes mellitus²⁹. Because type II diabetes is caused by a combination of insulin resistance along with insulin insufficiency, it was expected that “diabetes genes” would map to beta cell function and insulin resistance. As of

2011, approximately 38 “diabetes genes” had been reported ²⁹. Surprisingly, the majority of these diabetes genes affect beta cells or are of unknown function. Only a few map to insulin resistance. Known genes that map to insulin resistance include the insulin receptor, IRS-1, glucokinase regulator, IGF-I, and PPAR γ ²⁹. It is expected that numerous additional “insulin resistance genes” are yet to be discovered, and that they will map to various components of the insulin signaling pathway.

It is also expected that pharmacogenomics investigations will also reveal insulin resistance pathways. One exciting development in this regard is the recent genome wide association study searching for genes required for metformin action ^{30,31}. Metformin has been used for many decades to treat type 2 diabetes because it sensitizes insulin target tissues. The study reported that the ATM (Ataxia Telangiectasia Mutated) gene is required for the action of metformin ^{30,31}. The ATM gene encodes a serine protein kinase that phosphorylates LKB1, an AMP-activated protein kinase (AMPK) kinase ³¹. This is important because AMPK is involved in the action of metformin and interfaces with the insulin signaling pathway ³¹.

Summary

Insulin has many physiological functions and its signaling pathways are tightly controlled through cross talk. The interplay of genes and lifestyle has led to the obesity epidemic, which underlies the epidemic of metabolic syndrome / insulin resistance syndrome. A large body of evidence indicates that the underlying etiology of the components of insulin resistance syndrome is in fact insulin resistance itself. The etiologies of insulin resistance are numerous and complex. They include hyperinsulinemia, hyperlipidemia leading to lipotoxicity, adipokines from adipose tissue, incretins from the gut, and cytokines from macrophages, all of which cross talk with insulin signaling pathways.

The “bedside to bench” theme of the symposium in 2011 stemmed from the recognition that interference with angiotensin signaling improves insulin sensitivity as discussed by Prabhakar³. This overview of insulin action and insulin resistance, along with an overview of angiotensin signaling by Navar⁴, provide the background for the subsequent descriptions of angiotensin– insulin cross talk by Folli² and Prabhakar³.

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Figure 1.

Two insulin-signaling pathways mediate numerous actions of insulin. The insulin receptor (IR) is a tetramer composed of two alpha and two beta subunits that span the plasma membrane. A single gene encodes the alpha and beta subunits (Gene ID: 3643), which are posttranslationally cleaved and held together by disulfide bonds. There are two pro-IR isoforms, a short and a long form (A and B, respectively), that arise through alternative splicing of exon 11. As a consequence, the alpha subunit of IR-B contains 12 additional amino acids at its C-terminus. These two isoforms are known to have differing functions³²⁻³⁴, which could be responsible for the separate metabolic (top) versus mitogenic (bottom) pathways illustrated here. In both pathways, insulin (I) binding activates an intrinsic tyrosine-protein kinase that autophosphorylates the receptor as well as downstream substrates including IRS (Insulin Receptor Substrates) or SHC (Src homology domain-containing protein). Additional details can be found in *Williams Textbook of Endocrinology*⁷.

Figure 2.

Adipocytes store and release triglyceride and regulate metabolism through secreted factors. Differentiation of preadipocytes into adipocytes requires the actions of the transcription factors $\text{PPAR}\gamma$ and C/EBPs. This figure illustrates the functions of white adipose tissue to store triglyceride (TG) and release it as glycerol and fatty acids (FAs) for use as fuel by tissues such as skeletal muscle. Some of the major adipokines, their physiological actions, and the consequences of obesity are shown. Adapted from Beale et al.¹¹ with permission from Elsevier.