Role of the IRS-1 and/or -2 in the pathogenesis of insulin resistance in Dahl salt-sensitive (S) rats

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Abstract

Insulin resistance is a common finding in hypertensive humans and animal models. The Dahl salt-sensitive (S) rat is an ideal model of genetically predetermined insulin resistance and salt-sensitive hypertension. Along the insulin signaling pathway, the insulin receptor substrates 1 and 2 (IRS-1 and -2) are important mediators of insulin signaling. IRS-1 and/or IRS-2 genetic variant(s) and/or enhanced serine phosphorylation correlate with insulin resistance. The present commentary was designed to highlight the significance of IRS-1 and/or -2 in the pathogenesis of insulin resistance. An emphasis will be given to the putative role of IRS-1 and/or -2 genetic variant(s) and serine phosphorylation in precipitating insulin resistance.

Insulin resistance is at the crossroads of the cardiometabolic syndrome

Insulin resistance is a disorder characterized by the improper utilization of glucose by the cells. This is because of an existing and/or acquired impairment of the cell's ability to respond to exogenous or endogenous insulin. This, in turn, results in β-cell compensation failure and excessive blood glucose levels in the midst of hyperinsulinemia.[1] Insulin resistant subjects are predisposed to a cluster of risk factors that increase their risk of having cardiovascular diseases. These risk factors include high blood pressure, obesity, type 2 diabetes, elevated triglycerides, and lowered high density lipoprotein cholesterol (HDL-C).[1] Alarmingly, over one third of Canadian adults have insulin resistance,[2] and about half of salt-sensitive subjects are insulin resistant.[3] These elevated numbers of insulin resistant cases reflect the enormous economic burden that comes from the treatment modalities of several comorbidities per patient. The molecular mechanism of insulin resistance in hypertension, particularly in salt-sensitive hypertension, is not fully characterized. Insulin resistance might lead to hypertension because of diminished insulin-induced vasodilation and the imbalance between its pressor and depressor effects.[1,4,5] In hypertension, there is resistance to the actions of insulin on glucose uptake, but no resistance to the renal and sympathetic actions of insulin.[6-9] These secondary actions of insulin form the basis of the insulin hypothesis of hypertension. This hypothesis proposes that the compensatory hyperinsulinemia that occurs with insulin resistance increases sodium reabsorption and sympathetic activity, which combine to cause an increased vascular resistance and an elevated arterial pressure.[6,10] Owing to the fact that insulin resistance in Dahl salt-sensitive (S) rats precedes salt-sensitive hypertension in this model, we directed our attention to highlighting the putative role of insulin receptor substrates 1 and 2 (IRS-1 and -2) genetic variants in the pathogenesis of insulin resistance in Dahl S rats.

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Key words: Dahl S rats, insulin resistance, salt-sensitivity, insulin signaling pathway, genetic contributors, molecular contributors.

Received for publication: 12 May 2009
Revision received: 4 September 2009.
Accepted for publication: 4 September 2009.

Heart International 2009; 4:e6
doi:10.4081/hi.2009.e6

Insulin resistance in Dahl S rats

Dahl S rats represent an ideal model of insulin resistance syndrome because of its genetically predetermined insulin resistance,[11,12] hypertriglyceridemia, abdominal obesity, and salt-sensitive hypertension.[11] Regarding insulin concentrations, Dahl rats in general have higher values for insulin concentration than control Sprague Dawley rats implying their increased genetic susceptibility to insulin resistance.[11] Additionally, Dahl S rats have an increased serum insulin response to an oral glucose load independent of different salt intakes compared to Dahl salt-resistant (R) rats.[13] Regarding insulin sensitivity, Dahl S rats have decreased sensitivity to insulin,[14] as evidenced by a decreased insulin-stimulated glucose uptake by skeletal muscles obtained from Dahl S vs. Dahl salt-resistant (R) rats.[14] Regarding insulin receptors distribution, number, and affinity, they were all comparable in skeletal muscle and kidney of Dahl S and -R rats,[15] with no change in binding parameters in either group on high or low salt chow.[15] Hepatic, muscular, and renal insulin receptor mRNA levels were comparable in Dahl S and -R rats fed either low or high salt chow.[15] Regarding the impact of salt diet, Dahl S vs. -R rats had significant insulin resistance on high salt diet (8% NaCl) for four weeks vs. normal salt diet.[14] Dahl S rats insulin resistance on a high salt diet was characterized by an activation of the early steps in insulin signaling.[14] On the other hand, salt retention was significantly greater at weeks 1 and 2 in insulin-infused vs. saline-infused Dahl S rats receiving 0.3% NaCl vs. Dahl R rats, where insulin did not influence sodium retention, mean arterial pressure, or plasma epinephrine.[16] In conclusion, genetic background and excessive sodium intake are key factors contributing to the development of insulin resistance and salt sensitive hypertension in Dahl S rats. The decreased sensitivity to insulin in this model may involve a post-receptor defect possibly a genetic variant(s) in the IRS-1 and/or IRS-2 that contribute to their susceptibility to insulin resistance.[12,17]

Insulin receptor substrates -1 and -2

Variations in candidate genes encoding IRS-1 and -2 proteins involved in the insulin signaling pathway may be implicated in insulin resistance. Insulin actions in skeletal muscles, liver, kidney, fat, and brain result in increased renal sodium retention, modulation of transmembrane cation transport, induction of growth promoting effects of vascular smooth muscle cells, and vascular hyperreactivity.[18] The insulin signal transduction pathway is initiated when insulin binds to a high-affinity heterotetrameric transmembrane protein receptor that is present in all mammalian cells.[4,18] The insulin-receptor complex then triggers tyrosine phosphorylation of second

messengers, also called docking proteins, such as the insulin receptor substrates-1, -2, -3, and 4 (IRS-1, -2, -3, and -4).[19-22] This in turn activates the phosphoinositide 3 kinase (PI3K) enzyme, the activation of which stimulates the serine phosphorylation of Akt (Protein kinase B).[18] The latter enzyme (PKB) stimulates glucose transport in muscle and adipose tissue through the translocation of the glucose transporter GLUT4 isoform from the cytoplasm to the plasma membrane.[23,24] PKB also stimulates glycogen synthesis in the liver and muscle, and stimulates lipogenesis in adipose tissue.[23,24] While IRS-3 and -4 play a role in cell growth and differentiation, IRS-1 and -2 play an important role in glucose metabolism. Genes encoding for IRS-1 and/or -2 therefore may represent attractive candidate genes to study for insulin resistance.

Associations between insulin resistance and common variants in *IRS-1* and *-2* have been reported in several human populations,[19,25-33] including obese Caucasian children and adults, Asian Indians, Mexicans, and African-Americans. Mechanisms underlying the contributions of *IRS-1* and/or *IRS*-2 variants to insulin resistance include[34]: (i) altered expression and/or function of IRS-1 and/or -2; (ii) diminished IRS-1 and/or -2 binding to the insulin receptor; (iii) hindered binding of IRS-1 and/or -2 variant(s) to the p85 regulatory subunit of the PI3-kinase and a decreased PI3-kinase activity. As a result, a decrease in GLUT4 translocation to the plasma membrane and a reduced glucose transport and glycogen synthesis will ensue. Additionally, an impairment in the ability of IRS-1 and/or -2 to decrease phosphorylation of glycogen synthase kinase-3 (GSK-3), an enzyme that is important in glycogen synthesis, will reduce glycogen synthesis; and (iv) decreased IRS-1 protein levels that are not counterbalanced by a concomitant increase in the IRS-2 protein content. This, in turn, causes a reduction in insulin-stimulated PI3-kinase activity and a significant decrease in Akt phosphorylation and activity. In conclusion, IRS-1 and/or -2 variant(s) appear to contribute to the impaired ability of insulin to activate the IRS/PI3-kinase/Akt/GSK-3 signaling pathway, which ultimately results in defects in glucose transport and glycogen synthesis.

Is it the IRS-1 and/or -2 genetic variations, or the enhanced IRS-1 and/or -2 serine phosphorylation, or both that predispose Dahl S rats to insulin resistance?

IRS-1 and -2 tyrosine phosphorylation activates IRS proteins to bind to signaling molecules in the insulin signaling pathway (such as PI3K).[20,21] On the other hand, serine phosphorylation of IRS proteins attenuates insulin signaling and explains an additional mechanism of insulin resistance in rodents.[35] For example, increased serine phosphorylation of IRS-1 was demonstrated in the liver of an insulin resistant rat model,[35] supporting the role of serine phosphorylation in precipitating insulin resistance in this model. Owing to the fact that IRS proteins have three times more serine residues than tyrosine residues,[3,1] the significance of serine phosphorylation has been markedly highlighted. Serine phosphorylation of IRS-1 and IRS-2 can suppress insulin signaling[36-39] in the following ways: it can (i) allow dissociation of IRS proteins from the insulin receptor; (ii) diminish tyrosine phosphorylation on usual sites by covering up phosphorylation sites and enhancing the release of IRS proteins from intracellular complexes that maintain them in close proximity to the receptor; (iii) enhance IRS proteolytic degradation; or (iv) switch IRS proteins to inhibitors of the insulin receptor.

It is worth mentioning at this point that Dahl S rats have chronic hyperinsulinemia,[11] which potentially might enhance serine phosphorylation of IRS-1 and/or -2[39] and possibly explain an additional mechanism of insulin resistance in Dahl S rats.

Perspectives

Knowledge of which genetic variants along the insulin signaling pathway are important in the genesis of salt-dependent insulin resistance (a disease that comprises a large subgroup [over 30%] of Canadian adults) would enhance the understanding of the basic pathophysiology of the disease. In addition it may create one or more specific targets for the development of a novel anti-insulin resistance drug or gene therapy. Variations in genes encoding the IRS-1 or -2 proteins might be at the level of DNA (genetic variants) or at the level of serine phosphorylation as explained above.

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