BIOCHEMICAL MECHANISMS UNDERLYING IMPAIRED INSULIN SIGNAL TRANSDUCTION IN INSULIN RESISTANCE

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Relevance: Insulin resistance (IR) represents a fundamental pathophysiological condition contributing to the onset and progression of type 2 diabetes, obesity, and metabolic syndrome. Although circulating insulin concentrations are often normal or elevated, target tissues exhibit diminished responsiveness to insulin signaling. This defect results in compromised glucose uptake, dysregulated metabolic processes, and enhanced hepatic gluconeogenesis. Furthermore, IR is frequently associated with a state of chronic low-grade inflammation, which exacerbates metabolic dysfunction.

Objective: The present study seeks to systematically examine the principal biochemical and molecular mechanisms responsible for impaired insulin signal transduction. Particular emphasis is placed on alterations in insulin receptor functionality, dysregulation of insulin receptor substrate (IRS) proteins, attenuation of the PI3K/Akt signaling cascade, and the contributory roles of oxidative stress, inflammatory pathways, and lipid-induced cellular toxicity.

Materials and Methods: This investigation is based on a comprehensive review of experimentally validated studies addressing the molecular basis of insulin resistance. The analyzed data were derived from human clinical research, obesity-induced animal models, and in vitro experimental systems, including skeletal muscle cell lines (C2C12, L6), adipocytes (3T3-L1), and hepatocytes (HepG2).

The analysis focused on critical molecular parameters such as phosphorylation status of the insulin receptor and IRS proteins, activity of the PI3K/Akt signaling pathway, and the efficiency of GLUT4 vesicle translocation. Additionally, key metabolic and biochemical indicators—including glucose uptake rates, oxidative stress biomarkers (ROS, MDA, SOD, GSH), and concentrations of pro-inflammatory cytokines—were systematically evaluated. These integrated approaches facilitate a deeper understanding of how metabolic overload and ectopic lipid accumulation disrupt intracellular insulin signaling networks.

Expected Results: Current evidence indicates that insulin resistance is closely associated with defects in insulin receptor-mediated signaling and aberrant regulation of IRS proteins. In particular, enhanced serine phosphorylation of IRS molecules appears to

impair downstream signaling efficiency by inhibiting PI3K/Akt pathway activation. This disruption leads to reduced GLUT4 translocation to the plasma membrane and consequently diminished glucose uptake in insulin-sensitive tissues. Concurrently, hepatic glucose output is elevated, while persistent metabolic stress further aggravates insulin resistance.

Conclusion: Insulin resistance arises from a complex interplay of molecular abnormalities, including impaired IRS-mediated signaling, suppression of the PI3K/Akt pathway, oxidative stress, and chronic inflammation. These interrelated mechanisms collectively disturb glucose homeostasis and significantly contribute to the pathogenesis of type 2 diabetes. Elucidating these pathways may provide a theoretical foundation for the development of targeted therapeutic strategies aimed at restoring insulin sensitivity and improving metabolic outcomes.