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Review article

Animal models of insulin resistance: A review

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ABSTRACT

Insulin resistance can be seen as a molecular and genetic mystery, with a role in the pathophysiology of type 2 diabetes mellitus. It is a basis for a number of chronic diseases like hypertension, dyslipidemia, glucose intolerance, coronary heart disease, cerebral vascular disease along with T2DM, thus the key is to cure and prevent insulin resistance. Critical perspicacity into the etiology of insulin resistance have been gained by the use of animal models where insulin action has been modulated by various transgenic and non-transgenic models which is not possible in human studies. The following review comprises the pathophysiology involved in insulin resistance, various factors causing insulin resistance, their screening and various genetic and non-genetic animal models highlighting the pathological and metabolic characteristics of each.

Contents

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Introduction

Diabetes mellitus is a globally prevalent metabolic disorder of major concern nowadays. Over the last few years, the incidence and prevalence of type 2 diabetes has increased dramatically suggesting that changes in environment and life style are the major contributors. The World Health Organization estimates that 346 million people worldwide have diabetes [1]. India, the diabetes capital of the world has largest population of diabetics which is rising day by day [2]. Insulin resistance (IR) and impaired insulin secretion are principal implications in the pathogenesis of type 2 diabetes [3]. Insulin resistance is a complex metabolic abnormality and common concern in prediabetics and diabetics, that affects ability of peripheral tissues to use insulin, thus impairing peripheral glucose utilization and resulting in development of hyperglycemia and/or compensatory hyperinsulinemia [4]. The main peripheral tissues involved are liver, skeletal muscle and adipose tissue as they are main insulin sensitive sites. Among them, liver has important role in determining fasting hyperglycemia hence hepatic insulin resistance is a prediabetic state [5]. It forces β cell to continuously hyper secrete insulin which eventually leads to progressive β cell failure of type 2 diabetes [6].

In insulin resistance biochemical parameters like blood glucose level, blood triglyceride level, and blood cholesterol level increases whereas blood HDL cholesterol level decreases and thus contributing to cardiovascular disease and metabolic syndrome [7]. The etiology of insulin resistance is multifactorial including genetic and environment factors. Epidemiological studies suggest that insulin resistance is a basis for a number of chronic diseases like hypertension, dyslipidemia, glucose intolerance, coronary heart disease, cerebrovascular disease along with T2DM, as it affects body's whole metabolism. Thus the key is to cure and prevent insulin resistance.

Available therapeutic strategies for type 2 diabetes and insulin resistance are associated with problems of improper efficacy and side effects. So, there is a continuous ongoing research for improved medications for diabetes and insulin resistance. Hence various animal models are being developed and studied to understand the influence of environment and genes on insulin action, causing insulin resistance. The aim of this review, is to give an overview of the currently available animal models of insulin resistance to be used in testing various classes of new chemical entities.

Overview of insulin action and pathophysiology of insulin resistance

Insulin receptor belongs to a subfamily of receptor tyrosine kinases. The receptor is heterotetrameric glycoprotein with two extracellular α-subunits and two transmembrane β subunits with tyrosine kinase activity. Insulin binds to α subunits and subsequently receptor gets autophosphorylated at specific tyrosine residues of the insulin receptor β-subunit. This in turn translocates insulin receptor substrate (IRS)-1 to the plasma membrane where it interacts with the insulin receptor to undergo tyrosine phosphorylation [6]. This stimulates binding of IRS to p85, the regulatory subunit of phosphatidyl (PI)-3-kinase (PI3-K) leading to (PI)-3-K activation. Activated PI-3 kinase further activates PI3K-dependent kinases, such as Pdk1 [3]. Pdk1 then phosphorylates and activates additional serine/threonine kinases (three Akt isoforms) [8]. Activated Akt leads to activation of glycogen synthesis and translocates glucose transporter 4 to the cell membrane for glucose entry into the cel1 (Fig. 1).

Alteration of these signal proteins in the form of phosphorylation and dephosphorylation, from the insulin receptor to any downstream signal proteins such as Akt, may affect insulin action resulting in insulin resistance. Manifestations at the cellular level include down-regulation, deficiencies or polymorphisms of tyrosine phosphorylation of the insulin receptor, IRS proteins or PI3 kinase, impaired Akt activation or abnormalities of GLUT 4 function [9]. Tyrosine phosphatase 1β dephosphorylates insulin receptor that also leads to insulin resistance.

Several studies demonstrate the role of proinflammatory cytokines and endoplasmic stress in causing insulin resistance through activation of serine kinases c-Jun N-terminal kinase (JNK) and I kappa B kinase (IKK-β) that promote phosphorylation of IRS-1 at serine sites (serine 302 pS302 and serine 307 pS307) that negatively regulate normal insulin signaling [10]. Moreover activated IKK-β phosphorylates IκB protein, which is an inhibitor of nuclear factor kappa β (NFkβ) a transcription factor. Phosphorylation of Iκβ in response to inflammatory cytokines, targets it for proteosomal degradation which releases NFκβ. NFκβ then translocates into the nucleus and promotes expression of various target genes whose products induce insulin resistance.

Obesity and consumption of saturated fats also activates JNK. Increased lipid deposition in adipocyte in obesity leads to the production of proinflammatory cytokines including TNFα, IL-6, IL-1β and resistin which further activate JNK and NFκβ pathways [11,12]. Hence obesity induced activation of NFκβ enhances inflammatory responses that exacerbate insulin resistance. Adipokine resistin induces Suppressor of Cytokine Signaling (SOCS) family proteins which induces insulin resistance by interfering with IRS-1 and IRS-2 tyrosine phosphorylation or by targeting IRS-1 and IRS-2 for proteosomal degradation [12]. Another mechanism related to obesity-associated insulin resistance is increase in intracellular metabolites (diacylglycerol) triggered by fatty acids, that activate protein kinase C (PKC), leading to the activation of serine/threonine kinases that further impair IRS tyrosine phosphorylation. Dietary lipids also activate Toll-like receptor (TLR), which defends against infectious agents. Activated TLR's mediates inflammatory responses