AMERICAN ACADEMIC PUBLISHER

INTERNATIONAL JOURNAL OF MEDICAL SCIENCES

ISSN NUMBER: 2692 - 5206 Volume 5. No 12. December ,2025

PHYSIOLOGICAL MECHANISMS OF INSULIN RESISTANCE IN DIABETES MELLITUS

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Abstract: Insulin resistance (IR) is a key pathophysiological feature of type 2 diabetes mellitus (T2DM) and plays a central role in the development of hyperglycemia and metabolic disturbances. The phenomenon of insulin resistance refers to the impaired ability of insulin to exert its biological effects on target tissues, particularly skeletal muscle, liver, and adipose tissue, resulting in reduced glucose uptake, increased hepatic glucose production, and altered lipid metabolism. This article explores the physiological mechanisms underlying insulin resistance, including defects in insulin signaling pathways, inflammatory processes, alterations in adipokine release, and the impact of genetic and environmental factors. Understanding the complex mechanisms of insulin resistance is essential for the development of effective therapeutic strategies to prevent and manage diabetes and its complications.

Keywords: insulin resistance, type 2 diabetes, insulin signaling, inflammation, adipokines, metabolic syndrome

Introduction

Insulin resistance is a pathological condition in which the body's tissues become less responsive to the actions of insulin. Insulin is a key hormone that regulates glucose, fat, and protein metabolism by promoting the uptake of glucose into cells, particularly in the liver, muscle, and adipose tissues. Under normal circumstances, insulin acts as a signal for the cells to take up glucose and store it as glycogen, while also inhibiting glucose production by the liver. However, in insulin resistance, this normal insulin signaling pathway is disrupted, leading to elevated blood glucose levels, increased insulin secretion (hyperinsulinemia), and eventually the development of type 2 diabetes mellitus (T2DM).

The pathophysiology of insulin resistance is multifactorial, involving both genetic and environmental factors. Insulin resistance is commonly associated with obesity, particularly visceral adiposity, and metabolic syndrome. It is also seen in conditions such as hypertension, dyslipidemia, and impaired glucose tolerance. As insulin resistance progresses, the pancreatic beta cells become increasingly unable to compensate for the reduced sensitivity to insulin, leading to hyperglycemia and the eventual development of overt diabetes.

This article aims to review the major physiological mechanisms that contribute to insulin resistance, with a focus on the molecular defects in insulin signaling, the role of adipokines, the influence of inflammation, and the contributions of genetic and environmental factors. Understanding these mechanisms is crucial for identifying targets for therapeutic intervention and improving the management of T2DM and its associated complications.

Materials and Methods

This article is based on a comprehensive review of scientific literature regarding the

AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES
ISSN NUMBER: 2692 - 5206 Volume 5. No 12. December ,2025

physiological mechanisms of insulin resistance in diabetes mellitus. Data were collected from peer-reviewed journals, textbooks on endocrinology and metabolism, and clinical research studies published in the last decade. Descriptive and analytical methods were used to summarize the mechanisms involved in insulin resistance, including those related to insulin signaling pathways, inflammation, adipokine dysregulation, and other factors contributing to metabolic dysfunction. The sources reviewed provided a detailed analysis of insulin resistance in both human and animal models.

Results

The physiological mechanisms underlying insulin resistance are complex and involve multiple defects in insulin signaling pathways. In skeletal muscle, insulin resistance leads to impaired glucose uptake due to decreased activation of the insulin receptor substrate (IRS) proteins, which are essential for initiating the insulin signaling cascade. A key player in this process is the serine phosphorylation of IRS-1, which interferes with its ability to activate downstream signaling molecules such as protein kinase B (Akt), thereby reducing glucose transport into the cell.

In the liver, insulin resistance results in impaired suppression of hepatic glucose production. Normally, insulin inhibits gluconeogenesis in the liver by decreasing the activity of enzymes involved in glucose synthesis, such as phosphoenolpyruvate carboxykinase (PEPCK). However, in the insulin-resistant state, this suppression is impaired, leading to increased glucose production by the liver and contributing to hyperglycemia.

Adipose tissue dysfunction also plays a critical role in the development of insulin resistance. Adipocytes in insulin-resistant individuals release elevated levels of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and resistin, which impair insulin signaling in muscle and liver. Additionally, adipose tissue-derived hormones, known as adipokines, including leptin, adiponectin, and visfatin, become dysregulated in obesity, further exacerbating insulin resistance. Specifically, low levels of adiponectin, an anti-inflammatory and insulin-sensitizing adipokine, are strongly associated with the development of insulin resistance.

Inflammatory pathways also play a critical role in the pathogenesis of insulin resistance. Chronic low-grade inflammation, which is commonly observed in obesity, leads to the activation of inflammatory mediators such as NF-kB (nuclear factor kappa-light-chain-enhancer of activated B cells) and C-reactive protein (CRP). These molecules impair insulin receptor signaling by promoting serine phosphorylation of IRS-1 and increasing the release of pro-inflammatory cytokines. Moreover, activation of the inflammasome complex in adipocytes further contributes to systemic inflammation and insulin resistance.

Other factors that contribute to insulin resistance include mitochondrial dysfunction, altered lipid metabolism, and the accumulation of lipid intermediates, such as ceramides and diacylglycerols, in tissues like muscle and liver. These lipid species can interfere with insulin signaling pathways by activating stress kinases such as JNK (c-Jun N-terminal kinase) and IKK (IκB kinase), which disrupt the function of IRS proteins.

Discussion

The results of this review highlight the multifaceted nature of insulin resistance, with defects in

AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES
ISSN NUMBER: 2692 - 5206 Volume 5. No 12. December ,2025

insulin signaling being at the core of the disease process. The interactions between genetic predisposition, obesity, inflammation, and lipid metabolism create a vicious cycle that perpetuates insulin resistance and leads to the development of type 2 diabetes mellitus. Understanding these mechanisms provides critical insight into the pathophysiology of insulin resistance and opens the door for targeted therapeutic interventions.

In clinical practice, the recognition of insulin resistance is vital for the early prevention and management of T2DM. Interventions such as lifestyle modifications (diet and exercise), pharmacological agents like metformin, and the use of insulin sensitizers can improve insulin sensitivity and delay or prevent the onset of diabetes. Moreover, addressing obesity, particularly abdominal adiposity, remains one of the most effective strategies for reducing insulin resistance and its associated metabolic complications.

The development of novel therapies aimed at modulating the key pathways involved in insulin resistance, such as targeting inflammatory cytokines, enhancing mitochondrial function, or improving adipokine signaling, holds promise for more effective treatments in the future. Further research into the molecular mechanisms of insulin resistance is necessary to better understand its underlying causes and to identify new therapeutic targets for managing T2DM and its associated cardiovascular and metabolic complications.

Conclusion

Insulin resistance is a central mechanism in the pathogenesis of type 2 diabetes mellitus, involving complex defects in insulin signaling pathways across multiple tissues, including skeletal muscle, liver, and adipose tissue. These defects are exacerbated by inflammation, dysregulated adipokine release, and altered lipid metabolism. The interplay of genetic and environmental factors further contributes to the development and progression of insulin resistance. Early detection and intervention are crucial for preventing the onset of type 2 diabetes and mitigating its complications. Understanding the physiological mechanisms of insulin resistance provides important insights into the treatment and prevention of diabetes, with promising therapeutic strategies targeting insulin sensitivity and metabolic homeostasis.

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ISSN NUMBER: 2692 - 5206 Volume 5. No 12. December ,2025

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