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MECHANISMS OF INSULIN ACTION AND INSULIN RESISTANCE

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Abstract. Insulin, a critical hormone produced by the beta cells of the pancreas, plays a central role in maintaining glucose homeostasis and regulating various metabolic processes in the human body. Understanding the mechanisms of insulin action and the development of insulin resistance is of utmost importance, given the rising prevalence of insulin-related disorders, such as type 2 diabetes and metabolic syndrome. This comprehensive review article aims to provide a detailed overview of the mechanisms underlying insulin's actions and the factors contributing to insulin resistance. The molecular structure of insulin and its interactions with specific cell surface receptors are explored, shedding light on the intricacies of insulin signaling pathways within cells. Emphasis is placed on the diverse intracellular effects of insulin, including glucose transport and metabolism, protein and lipid synthesis, as well as cell growth and proliferation. The article delves into the multifaceted nature of insulin resistance, discussing its definition and outlining various causes, including genetic predisposition, obesity, physical inactivity, and dietary habits. Moreover, the molecular mechanisms responsible for the impaired response to insulin are elucidated, with a particular focus on alterations in insulin receptor signaling and disruptions in intracellular pathways. Insulin resistance carries significant health implications, and this article addresses the consequences of insulin resistance, particularly its association with the development of type 2 diabetes and its links to cardiovascular diseases and other metabolic disorders. Furthermore, potential strategies to enhance insulin sensitivity and combat insulin resistance are presented. The role of lifestyle modifications, pharmacological interventions, and emerging therapeutic approaches in improving insulin sensitivity is discussed.

Keywords: *Insulin, pancreas, metabolism, protein.*

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1. Introduction

Insulin, a fundamental peptide hormone secreted by the beta cells of the pancreas, is a pivotal regulator of glucose homeostasis and a master orchestrator of various metabolic processes in the human body. Discovered nearly a century ago, the significance of insulin in maintaining normal physiological function has remained paramount in the field of endocrinology and metabolism. It plays a vital role in facilitating glucose uptake into cells, promoting energy storage, and modulating key anabolic and catabolic pathways.

The discovery of insulin and its life-saving potential revolutionized the management of diabetes mellitus, a condition characterized by hyperglycemia due to inadequate insulin secretion or impaired insulin action. Since then, extensive research

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efforts have been dedicated to unraveling the intricacies of insulin's mechanisms of action and its role in health and disease (Wei *et al*., 1995). This review article aims to provide a comprehensive examination of the mechanisms underlying insulin action and delve into the phenomenon of insulin resistance—a condition in which cells exhibit reduced responsiveness to the effects of insulin. Insulin resistance is now recognized as a critical factor in the pathogenesis of type 2 diabetes, a global health burden affecting millions of individuals worldwide. Additionally, insulin resistance is associated with an increased risk of cardiovascular diseases and other metabolic disorders, underscoring its clinical significance beyond diabetes.

The understanding of insulin action and the factors contributing to insulin resistance is pivotal for the development of novel therapeutic strategies to tackle insulin-related disorders effectively. By exploring the molecular basis of insulin's effects and the underlying causes of insulin resistance, we can identify potential targets for intervention and work towards improving patient outcomes and overall public health.

Throughout this article, we will examine the molecular structure of insulin and its interactions with cell surface receptors, shedding light on the intricate signaling cascades that underlie its biological effects. We will delve into the diverse intracellular mechanisms by which insulin exerts its actions, emphasizing its roles in glucose metabolism, protein synthesis, lipid metabolism, and cellular growth (Youngren, 2007).

Furthermore, we will discuss the multifactorial nature of insulin resistance, considering genetic predisposition, lifestyle factors, and environmental influences as key contributors to its development. By elucidating the molecular pathways involved in insulin resistance, we hope to gain insights into potential therapeutic avenues and preventive measures to combat this growing health concern.

In conclusion, this review aims to provide a comprehensive overview of the mechanisms of insulin action and insulin resistance, highlighting their importance in health and disease. By advancing our understanding of these processes, we aspire to pave the way for innovative approaches to address insulin-related disorders and ultimately improve the quality of life for individuals affected by these conditions (Bedinger & Adams, 2015).

2. Role and Importance of Insulin

Insulin, often referred to as the "master hormone," plays a central role in regulating glucose metabolism and maintaining overall energy balance in the human body. Produced and secreted by the beta cells of the pancreas, insulin exerts a multitude of essential functions, impacting various tissues and organs throughout the body. Its primary role is to facilitate the uptake, utilization, and storage of glucose, the body's primary source of energy, in response to changes in blood glucose levels (Youngren, 2007).

Glucose Regulation: One of the most critical roles of insulin is to regulate blood glucose levels. When we consume carbohydrates, they are broken down into glucose and released into the bloodstream. Elevated blood glucose levels trigger the release of insulin from the pancreas, which then facilitates the uptake of glucose into cells, particularly muscle and adipose (fat) tissues. This process ensures that cells receive the necessary energy to function correctly and that blood glucose levels are kept within a narrow range, preventing hyperglycemia (high blood sugar).

Glycogen Synthesis: Insulin also promotes the conversion of excess glucose into glycogen, a stored form of glucose, primarily found in the liver and muscle cells. Glycogen serves as a readily available energy reserve, which can be mobilized during periods of increased energy demand or when blood glucose levels drop, preventing hypoglycemia (low blood sugar).

Protein Synthesis: Beyond its role in glucose metabolism, insulin is involved in promoting protein synthesis in various tissues. It enhances the uptake of amino acids into cells, supporting the building and repair of proteins, essential for tissue growth, maintenance, and repair (Hubbard, 2013).

Lipid Metabolism: Insulin influences lipid metabolism by promoting the storage of excess fatty acids as triglycerides in adipose tissue. It also inhibits the breakdown of stored fats (lipolysis), ensuring a continuous supply of fatty acids for energy utilization during periods of fasting.

Cellular Growth and Differentiation: Insulin is crucial for cellular growth and differentiation, particularly during development and tissue repair processes. It supports cell proliferation, differentiation, and survival, contributing to overall tissue health and regeneration.

Appetite Regulation: Insulin's actions extend beyond its metabolic roles, as it also interacts with the brain to regulate appetite and satiety. After a meal, rising insulin levels signal to the brain that the body has received enough nutrients, leading to a feeling of fullness and reduced appetite (Araki *et al.,* 1994; Sun *et al.,* 1991).

1.1. Intracellular Mechanisms of Insulin's Action

Insulin's actions are mediated through a complex network of intracellular signaling pathways that orchestrate its effects on various tissues and metabolic processes. Upon binding to its cell surface receptors, insulin initiates a cascade of events that culminate in a cellular response. Understanding these intracellular mechanisms is crucial for unraveling the intricate ways insulin regulates glucose homeostasis, protein synthesis, lipid metabolism, and cellular growth.

Insulin exerts its effects by binding to specific insulin receptors located on the surface of target cells. The insulin receptor is a transmembrane receptor tyrosine kinase, consisting of two alpha subunits and two beta subunits linked together. Insulin binding to the alpha subunits induces a conformational change, leading to autophosphorylation of specific tyrosine residues in the beta subunits. This autophosphorylation activates the receptor's tyrosine kinase activity, initiating the signaling cascade (White, 2012).

Phosphorylated tyrosine residues on the activated insulin receptor serve as docking sites for a class of intracellular proteins called insulin receptor substrates (IRS). Once recruited to the receptor, IRS proteins are phosphorylated by the receptor's tyrosine kinase activity, allowing them to initiate downstream signaling events.

One of the primary pathways involved in mediating insulin's metabolic effects is the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) pathway. Phosphorylated IRS proteins activate PI3K, which then generates phosphatidylinositol-3,4,5-trisphosphate (PIP3) from phosphatidylinositol-4,5-bisphosphate (PIP2). PIP3 serves as a second messenger, recruiting AKT to the cell membrane, where it is activated by phosphorylation. Active AKT regulates multiple downstream targets, promoting glucose uptake through the translocation of glucose transporter 4 (GLUT4)

to the cell membrane and inhibiting enzymes involved in gluconeogenesis and glycogenolysis, thereby reducing blood glucose levels.

Insulin also activates the mitogen-activated protein kinase (MAPK) pathway through the recruitment and phosphorylation of another class of intracellular proteins called growth factor receptor-bound protein 2 (GRB2) and Son of Sevenless (SOS). This pathway is involved in insulin's role in cell growth, proliferation, and differentiation (Hubbard, 2013).

In insulin-sensitive tissues, such as skeletal muscle and adipose tissue, insulin stimulates glucose uptake by promoting the translocation of GLUT4 transporters to the cell membrane. Once inside the cells, glucose is metabolized through glycolysis and oxidative phosphorylation to generate energy or converted to glycogen for storage.

Insulin's activation of AKT stimulates protein synthesis by enhancing the translation of mRNA into proteins and inhibiting protein degradation. This process supports tissue growth, repair, and maintenance.

Insulin plays a crucial role in lipid metabolism by inhibiting the breakdown of stored triglycerides (lipolysis) in adipose tissue. It also promotes the synthesis of fatty acids and their conversion into triglycerides for storage.

The coordination of these intracellular mechanisms enables insulin to regulate a wide range of metabolic processes essential for maintaining cellular function and energy balance. Dysregulation of these pathways can lead to insulin resistance, impairing insulin's ability to exert its effects and contributing to the development of metabolic disorders such as type 2 diabetes. The intracellular mechanisms of insulin's action form a complex and finely tuned signaling network that enables insulin to regulate glucose metabolism, protein synthesis, lipid metabolism, and cellular growth. Understanding these mechanisms is critical for comprehending the pathophysiology of insulin-related disorders and developing targeted therapeutic interventions to restore insulin sensitivity and metabolic balance (Hsu *et al*., 2011).

1.2. Glucose Transport and Metabolism

Glucose, a fundamental carbohydrate and the primary energy source for cells, is transported into cells through a highly regulated process to meet the energy demands of various tissues. Glucose transport and metabolism are tightly coordinated to ensure that cells have a constant supply of this vital fuel while maintaining glucose homeostasis in the bloodstream (Petersen & Shulman, 2018).

The transport of glucose across cell membranes is facilitated by a family of glucose transporter proteins called GLUTs. Different tissues express specific GLUT isoforms with varying affinities for glucose and distinct regulatory properties. The most well-known GLUT isoform is GLUT4, primarily found in insulin-sensitive tissues such as skeletal muscle and adipose tissue. Under the influence of insulin, GLUT4 is translocated from intracellular vesicles to the cell membrane, increasing the uptake of glucose into these tissues. In insulin-sensitive tissues, such as skeletal muscle and adipose tissue, insulin plays a central role in promoting glucose uptake. Upon binding to its cell surface receptors, insulin activates intracellular signaling pathways, including the PI3K/AKT pathway. Activated AKT triggers the translocation of GLUT4 transporters from intracellular vesicles to the cell membrane, where they facilitate the entry of glucose into the cells. This insulin-mediated process ensures that glucose is effectively taken up by insulin-responsive tissues, reducing blood glucose levels (Mehran *et al*., 2012; Templeman *et al.,* 2015).

Some tissues, such as the brain, red blood cells, and kidney tubules, do not require insulin for glucose uptake. Instead, they rely on specific GLUT isoforms, such as GLUT1 and GLUT3 in the brain, which provide a constant supply of glucose without being influenced by insulin levels. This non-insulin-mediated uptake ensures that essential organs, such as the brain, receive a continuous supply of glucose to meet their energy demands. Once inside the cells, glucose undergoes a series of metabolic reactions to produce energy in the form of adenosine triphosphate (ATP) or stored as glycogen for future use. Glucose metabolism involves two main pathways:

- **Glycolysis:** In the cytoplasm, glucose is broken down through a series of enzymatic reactions into pyruvate. During glycolysis, a small amount of ATP and reducing equivalents (NADH) are generated, providing a quick source of energy for the cell.
- **Cellular Respiration:** Pyruvate is further metabolized within the mitochondria through oxidative phosphorylation, generating a larger amount of ATP. This process involves the citric acid cycle (Krebs cycle) and the electron transport chain, which utilize oxygen as the final electron acceptor.

In insulin-sensitive tissues and the liver, excess glucose can be converted into glycogen through a process called glycogenesis. Glycogen serves as a readily available energy reserve, particularly in times of increased energy demand or fasting when blood glucose levels decrease. Overall, glucose transport and metabolism are tightly regulated processes that play a crucial role in maintaining cellular energy balance and overall glucose homeostasis. Dysregulation of these processes, such as impaired insulin signaling or GLUT function, can lead to conditions like insulin resistance and diabetes, emphasizing the significance of understanding and maintaining glucose metabolism for overall health (Erion & Shulman, 2010; Gordon *et al.*, 2015; Petersen & Shulman, 2018; Samuel & Shulman, 2016).

1.3. Protein and Lipid Synthesis

In addition to its role in glucose metabolism, insulin also plays a pivotal role in regulating protein and lipid synthesis in various tissues throughout the body. These processes are essential for cell growth, repair, and maintenance, as well as the storage and utilization of lipids for energy.

Protein Synthesis:

Insulin stimulates protein synthesis in muscle and other tissues by activating the mammalian target of rapamycin complex 1 (mTORC1) pathway. When insulin binds to its receptor and activates the PI3K/AKT pathway, AKT in turn activates mTORC1. Activated mTORC1 then promotes protein synthesis by phosphorylating and activating key regulators of translation initiation, such as ribosomal protein S6 kinase (S6K) and eukaryotic initiation factor 4E-binding protein 1 (4E-BP1).

The activation of these translation initiation factors increases the assembly of ribosomes on mRNA transcripts, thereby enhancing the rate of protein synthesis. This process is crucial for tissue growth, repair, and *the synthesis of essential proteins required for various cellular functions* (Marchesini *et al*., 1999).

Lipid Synthesis:

Insulin plays a significant role in lipid metabolism, particularly in promoting lipid synthesis and storage in adipose tissue. Upon binding to its receptor and activating the PI3K/AKT pathway, insulin enhances the expression and activity of key enzymes involved in lipogenesis.

In adipocytes (fat cells), insulin stimulates the conversion of glucose into fatty acids through a process called de novo lipogenesis. This involves the conversion of glucose to acetyl-CoA, which serves as the building block for fatty acid synthesis. Subsequently, fatty acids are assembled into triglycerides for storage as lipid droplets in adipose tissue.

Insulin also inhibits lipolysis, the breakdown of stored triglycerides into free fatty acids and glycerol. By suppressing lipolysis, insulin helps to conserve energy and prevent the release of excess fatty acids into the bloodstream. Additionally, insulin promotes the uptake of fatty acids by adipose tissue and skeletal muscle, where they can be utilized for energy production through beta-oxidation, a process that occurs within the mitochondria (Morigny *et al*., 2016).

Overall, insulin's regulation of protein and lipid synthesis ensures a proper balance of macromolecules in cells, supporting growth, maintenance, and energy storage. Dysregulation of these processes can contribute to various metabolic disorders, including obesity and insulin resistance. In conclusion, insulin's role in protein and lipid synthesis is fundamental to cellular function and overall metabolic homeostasis. By modulating these processes, insulin contributes to tissue growth, repair, and energy utilization, maintaining the delicate balance required for optimal health. Understanding the mechanisms by which insulin regulates protein and lipid metabolism is essential for developing strategies to manage metabolic disorders and improve overall metabolic health (Goodpaster & Sparks, 2017).

1.4. Cell Growth and Proliferation

Insulin plays a critical role in regulating cell growth and proliferation, processes that are essential for tissue development, repair, and overall organismal growth. Insulin exerts its effects on cell growth and proliferation through intricate signaling pathways, ensuring proper tissue homeostasis and function.

Insulin stimulates cell growth by activating the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) pathway and the mammalian target of rapamycin complex 1 (mTORC1) pathway. As mentioned earlier, insulin binding to its receptor activates AKT, which, in turn, activates mTORC1.

The mTORC1 pathway is a central regulator of cell growth. When activated, mTORC1 promotes protein synthesis, as discussed previously, which contributes to an increase in cell size and mass. Additionally, mTORC1 stimulates ribosome biogenesis, enhancing the production of ribosomes, the cellular machinery responsible for protein synthesis. Furthermore, insulin-mediated activation of the AKT/mTORC1 pathway inhibits autophagy, a cellular process responsible for degrading damaged organelles and proteins. By suppressing autophagy, insulin ensures that cells can maintain their integrity and continue to grow (Muoio, 2014).

Insulin also influences cell proliferation, which refers to the process of cell division and reproduction. This is particularly important during growth and development, as well as tissue repair and regeneration.

Insulin activates the Ras/mitogen-activated protein kinase (MAPK) pathway, another critical signaling cascade involved in cell proliferation. Through the recruitment and phosphorylation of growth factor receptor-bound protein 2 (GRB2) and Son of Sevenless (SOS), insulin stimulates the Ras protein. Activated Ras then activates downstream signaling molecules, ultimately leading to the activation of MAPKs. The MAPK pathway promotes cell proliferation by stimulating the expression

of genes involved in cell cycle progression. This includes genes responsible for transitioning the cell from the resting (G0) phase to the proliferative phases (G1, S, G2, and M) of the cell cycle. The cell cycle ensures that cells replicate their genetic material and divide into two daughter cells with identical DNA.

By regulating cell growth and proliferation, insulin maintains tissue homeostasis, ensuring that cells can grow and divide when needed, while also preventing uncontrolled growth and proliferation that could lead to tumorigenesis or other pathological conditions. During periods of growth and development, insulin plays a critical role in regulating tissue growth and organ development. It facilitates the proliferation and differentiation of various cell types, contributing to the formation of tissues and organs with specialized functions (Rahimi *et al*., 2014).

Additionally, insulin is involved in tissue repair and regeneration. When tissues undergo damage due to injury or disease, insulin's actions on cell growth and proliferation aid in the restoration of tissue integrity and function. However, it's worth noting that dysregulated insulin signaling and persistent hyperinsulinemia (high levels of insulin in the blood) have been associated with certain cancers and other pathological conditions, highlighting the importance of maintaining insulin sensitivity and balanced insulin signaling. Insulin’s role in cell growth and proliferation is essential for tissue development, repair, and overall organismal growth. By activating specific signaling pathways, insulin ensures proper cell growth, division, and tissue homeostasis. Understanding the mechanisms underlying insulin's effects on cell growth and proliferation is crucial for comprehending the role of insulin in development, tissue repair, and the maintenance of overall health (Morino *et al.*, 2006; Summers & Nelson, 2005).

2. Definition and Causes of Insulin Resistance

Insulin resistance refers to a condition in which cells in the body become less responsive to the effects of insulin, resulting in a reduced ability of insulin to regulate glucose metabolism and other cellular processes effectively. As a consequence, higher levels of insulin are required to maintain normal glucose levels in the bloodstream. Insulin resistance is a hallmark feature of type 2 diabetes mellitus, but it can also occur in other metabolic conditions, such as obesity, metabolic syndrome, and polycystic ovary syndrome (PCOS). In this state, the body's tissues, particularly skeletal muscle, adipose tissue, and the liver, exhibit impaired insulin sensitivity. Consequently, glucose uptake into cells is reduced, leading to elevated blood glucose levels (hyperglycemia) and increased insulin production by the pancreas (hyperinsulinemia) (Perreault *et al*., 2018).

Insulin resistance not only disrupts glucose homeostasis but also affects other metabolic pathways, including lipid metabolism and protein synthesis. It can contribute to an array of adverse health effects, such as an increased risk of developing type 2 diabetes, cardiovascular diseases, and non-alcoholic fatty liver disease (NAFLD). Insulin resistance arises from a complex interplay of genetic, lifestyle, and environmental factors. Several key factors contribute to the development of insulin resistance: (Gaster, 2007; Gaster *et al.,* 2004).

- **Genetic Predisposition:** Genetics play a significant role in determining an individual's susceptibility to insulin resistance. Certain genetic variants can affect insulin signaling pathways or cellular responses to insulin, increasing the risk of

developing insulin resistance.

- **Obesity:** Obesity is one of the primary drivers of insulin resistance. Adipose tissue, particularly in the abdominal region, releases inflammatory cytokines and adipokines that interfere with insulin signaling in other tissues, contributing to insulin resistance. Additionally, excess adiposity alters the balance of hormones involved in appetite regulation and energy homeostasis, further exacerbating insulin resistance.

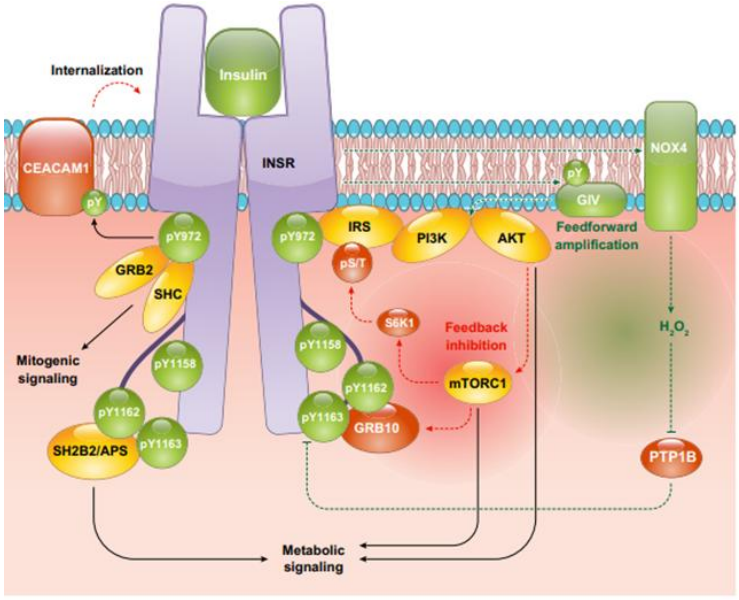

Fig. 1. Proximal insulin signaling. Upon insulin binding, the insulin receptor (INSR) autophosphorylates and recruits diverse substrates (Corpeleijn *et al*., 2009)

- **Sedentary Lifestyle:** Lack of physical activity and sedentary behavior are strongly associated with insulin resistance. Regular exercise enhances insulin sensitivity and glucose uptake in skeletal muscles, reducing the risk of insulin resistance.
- **Unhealthy Diet:** Diets high in refined carbohydrates, added sugars, and saturated fats can promote insulin resistance. Overconsumption of these types of foods can lead to chronically elevated blood glucose and insulin levels, contributing to insulin resistance over time.
- **Aging:** Aging is associated with a gradual decline in insulin sensitivity. As individuals age, their cells may become less responsive to insulin, increasing the risk of developing insulin resistance.
- **Inflammation:** Chronic low-grade inflammation, often observed in obesity and metabolic disorders, can interfere with insulin signaling pathways and promote insulin resistance.
- **Sleep Deprivation:** Chronic sleep deprivation or poor sleep quality has been linked to insulin resistance, possibly due to alterations in hormones that regulate appetite and metabolism.
- **Certain Medical Conditions:** Certain medical conditions, such as PCOS, acromegaly, and Cushing's syndrome, can lead to insulin resistance as a component of their underlying pathophysiology (DeFronzo & Tripathy, 2009).

Insulin resistance is a multifactorial condition resulting from a combination of genetic predisposition, lifestyle factors, and environmental influences. Addressing the causes of insulin resistance is crucial for preventing its progression to more severe metabolic disorders and improving overall metabolic health. Lifestyle modifications, including weight management, regular physical activity, and a balanced diet, are key components of managing insulin resistance and reducing the risk of related complications (DeFronzo & Tripathy, 2009; Shulman *et al*., 1990; Thiebaud *et al*., 1982).

3. Molecular Mechanisms of Insulin Resistance

Insulin resistance is a complex metabolic phenomenon involving a range of molecular mechanisms that impair insulin signaling and cellular responses to insulin. These mechanisms can occur at various levels of the insulin signaling pathway, leading to reduced glucose uptake, dysregulated lipid metabolism, and disrupted cellular growth and proliferation. Understanding these molecular mechanisms is crucial for identifying potential therapeutic targets and developing interventions to combat insulin resistance. One of the key molecular mechanisms underlying insulin resistance involves the serine phosphorylation of insulin receptor substrate (IRS) proteins. In insulin-sensitive tissues, IRS proteins are phosphorylated by the insulin receptor on specific tyrosine residues, initiating downstream signaling. However, under conditions of chronic hyperinsulinemia, increased levels of certain kinases can lead to the phosphorylation of IRS on serine residues instead of tyrosine (Boucher *et al*., 2014).

Serine phosphorylation of IRS impairs its ability to transmit insulin signaling, leading to reduced activation of the PI3K/AKT pathway. As a result, glucose uptake is decreased, and other insulin-mediated processes, such as lipid metabolism and protein synthesis, are affected. Elevated levels of free fatty acids, a common feature of obesity and insulin resistance, can activate protein kinase C (PKC) isoforms. PKC activation interferes with insulin signaling by phosphorylating insulin receptor tyrosine kinase and downstream insulin signaling molecules.

In particular, PKC-θ has been implicated in the development of insulin resistance in skeletal muscle, as it inhibits insulin signaling and impairs GLUT4 translocation to the cell membrane, reducing glucose uptake. Chronic low-grade inflammation, often observed in obesity, can contribute to insulin resistance. Adipose tissue secretes pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), which interfere with insulin signaling pathways. These cytokines activate intracellular kinases, such as c-Jun N-terminal kinase (JNK) and inhibitor of κB kinase (IKK), which promote serine phosphorylation of IRS proteins, further impairing insulin signaling. In addition, inflammation can also lead to increased production of reactive oxygen species (ROS), which can damage insulin signaling molecules and contribute to insulin resistance (Boucher *et al*., 2014).

Accumulation of lipids in non-adipose tissues, such as skeletal muscle and liver, can result in lipotoxicity, a condition in which excess lipids lead to cellular dysfunction and insulin resistance. Lipids, such as diacylglycerol (DAG) and ceramides, can activate PKC and other kinases, contributing to serine phosphorylation of IRS and impaired insulin signaling. Furthermore, lipids can interfere with mitochondrial function and promote endoplasmic reticulum (ER) stress, both of which can impair insulin signaling and contribute to insulin resistance (Pederson *et al*., 2001).

In adipose tissue, dysregulated lipolysis, the breakdown of stored triglycerides into free fatty acids and glycerol, can occur in insulin-resistant states. Increased lipolysis leads to elevated levels of free fatty acids in the bloodstream, which can promote insulin resistance in other tissues, such as skeletal muscle and liver. The excess free fatty acids can induce insulin resistance by impairing insulin signaling and promoting lipid accumulation in insulin-sensitive tissues. These molecular mechanisms of insulin resistance represent just a few of the complex processes involved in the development of this metabolic disorder. The interplay of genetic, environmental, and lifestyle factors contributes to the dysregulation of insulin signaling pathways and cellular responses to insulin, ultimately leading to insulin resistance and associated metabolic abnormalities. Targeting these molecular mechanisms holds promise for developing novel therapeutic approaches to improve insulin sensitivity and combat insulin resistance in various metabolic disorders (Pederson *et al.*, 2001).

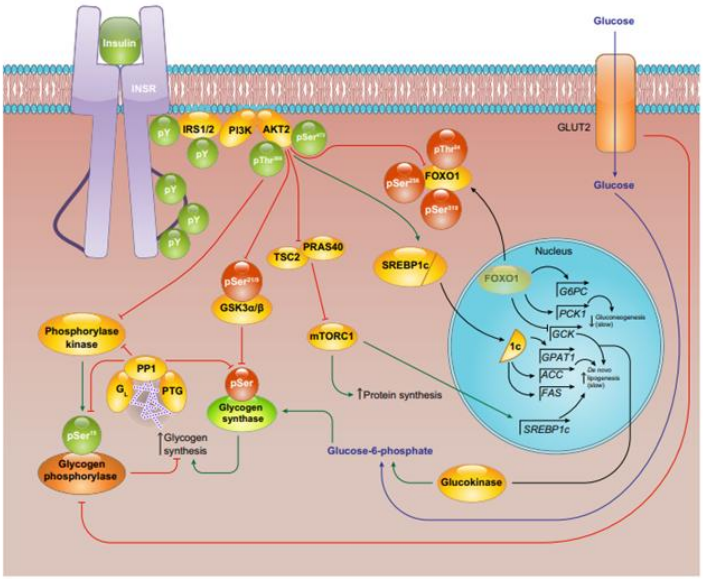

Fig. 2. Hepatic insulin signaling (DeFronzo & Tripathy, 2009; Taniguchi *et al*., 2006).

4. Consequences and Health Effects of Insulin Resistance

Insulin resistance is a central feature of various metabolic disorders and can have widespread consequences on health. It significantly impacts multiple organs and systems in the body, contributing to a range of adverse health effects. Understanding the consequences of insulin resistance is essential for recognizing its clinical significance and the importance of early intervention to prevent or manage related health conditions (Boucher *et al*., 2014).

Insulin resistance is a primary driver of type 2 diabetes mellitus. When cells become less responsive to insulin, the pancreas compensates by producing more insulin to maintain normal blood glucose levels. However, over time, the beta cells in the pancreas may become exhausted and fail to secrete sufficient insulin. This results in chronically elevated blood glucose levels (hyperglycemia), leading to the development of type 2 diabetes. Uncontrolled hyperglycemia can cause a range of complications, including damage to blood vessels, nerves, and organs. Insulin resistance is associated with an increased risk of developing cardiovascular diseases. Elevated insulin levels and

insulin resistance can promote atherosclerosis, the buildup of fatty plaques in arteries, leading to narrowed and hardened blood vessels. This condition increases the risk of heart attacks, strokes, and other cardiovascular events (Cho *et al*., 2001).

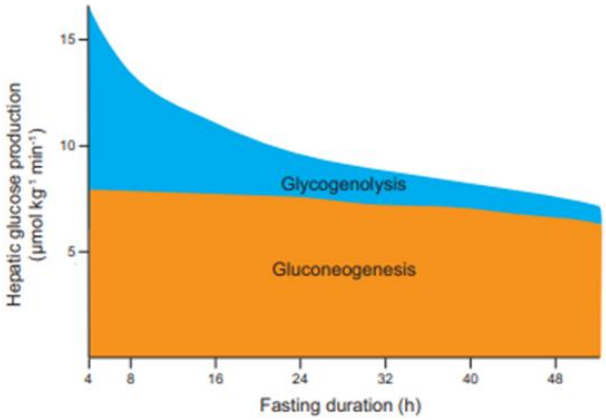

Fig. 3. Sources of hepatic glucose production during fasting in humans. During the early postprandial period (not shown), the liver performs net glucose uptake as ingested glucose is stored as liver glycogen (Gao *et al*., 2011)

Insulin resistance is also linked to hypertension (high blood pressure), dyslipidemia (abnormal lipid levels), and endothelial dysfunction, which further contribute to cardiovascular risk. Insulin resistance plays a central role in the development of non-alcoholic fatty liver disease (NAFLD), a condition characterized by excess fat accumulation in the liver. As insulin resistance progresses, the liver becomes less sensitive to insulin's inhibitory effect on lipolysis (the breakdown of stored fat). This leads to increased release of fatty acids into the liver, promoting hepatic lipid accumulation and the development of NAFLD. In some individuals, NAFLD can progress to more severe conditions, such as non-alcoholic steatohepatitis (NASH) and cirrhosis, with potential long-term consequences for liver function and health. Insulin resistance is a common feature of obesity and is a key component of metabolic syndrome—a cluster of metabolic abnormalities that include insulin resistance, hypertension, dyslipidemia, and central obesity. Metabolic syndrome increases the risk of developing type 2 diabetes and cardiovascular diseases, highlighting the importance of addressing insulin resistance in the context of obesity and metabolic disorders. Insulin resistance is prevalent in women with polycystic ovary syndrome (PCOS), a hormonal disorder characterized by irregular menstrual cycles, excessive hair growth, and enlarged ovaries with multiple small cysts. Insulin resistance in PCOS contributes to hyperinsulinemia, which disrupts ovarian function and increases androgen (male hormone) production. This can lead to hormonal imbalances, fertility issues, and other complications.

Insulin resistance and chronic hyperinsulinemia have been associated with an increased risk of certain types of cancer, such as breast, colon, and prostate cancer. Elevated insulin levels may promote tumor growth by stimulating cell proliferation and inhibiting apoptosis (programmed cell death). Emerging research suggests that insulin resistance may be linked to cognitive decline and an increased risk of Alzheimer's disease. Impaired insulin signaling in the brain can negatively affect neuronal function and synaptic plasticity, potentially contributing to cognitive impairment.

Insulin resistance has far-reaching consequences on health, affecting multiple organ systems and increasing the risk of various chronic diseases. Early detection and intervention to improve insulin sensitivity and manage insulin resistance are crucial for preventing or mitigating these health effects and promoting better metabolic health. Lifestyle modifications, including a balanced diet, regular physical activity, and weight management, are essential components of managing insulin resistance and its associated health risks (Cho *et al*., 2001b).

5. Treatment and Preventive Measures to Improve Insulin Sensitivity

Improving insulin sensitivity is a key goal in managing insulin resistance and preventing the progression of metabolic disorders, such as type 2 diabetes and cardiovascular diseases. Treatment and preventive measures focus on lifestyle modifications, pharmacological interventions, and targeted therapies aimed at enhancing insulin action and maintaining metabolic balance. Here are some effective strategies to improve insulin sensitivity. Weight Management: Achieving and maintaining a healthy body weight through a balanced diet and regular physical activity is essential for improving insulin sensitivity. Weight loss, particularly a in individual who are overweight or obese, has been shown to significantly enhance insulin sensitivity and reduce the risk of type 2 diabetes (Hausdorff *et al*., 1999).

Adopting a diet that is rich in whole, nutrient-dense foods, such as fruits, vegetables, whole grains, lean proteins, and healthy fats, can help improve insulin sensitivity. Reducing the intake of refined carbohydrates, added sugars, and saturated fats is beneficial in managing insulin resistance. Engaging in regular aerobic exercises, such as brisk walking, jogging, cycling, or swimming, can enhance insulin sensitivity in skeletal muscles and improve glucose uptake. Strength training exercises can also promote muscle mass and further improve insulin sensitivity. Adequate sleep and stress reduction are essential for maintaining insulin sensitivity. Chronic sleep deprivation and high-stress levels can negatively impact insulin action and glucose metabolism. Several classes of oral medications, such as metformin, sulfonylureas, thiazolidinediones, and dipeptidyl peptidase-4 (DPP-4) inhibitors, are commonly prescribed to manage insulin resistance and type 2 diabetes. These medications work through various mechanisms to improve insulin sensitivity and lower blood glucose levels. For individuals with advanced insulin resistance or type 2 diabetes that is poorly controlled by oral medications, insulin therapy may be prescribed to help regulate blood glucose levels and improve insulin sensitivity.

Incretin-based therapies, including glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors, enhance insulin secretion, suppress glucagon release, and slow gastric emptying. These actions can improve glucose control and insulin sensitivity. Sodium-glucose cotransporter 2 (SGLT2) inhibitors are a class of medications that promote the excretion of glucose in the urine, thereby lowering blood glucose levels and improving insulin sensitivity. For individuals with severe obesity and insulin resistance, bariatric surgery may be considered as a treatment option. Weight loss achieved through surgical interventions, such as gastric bypass or sleeve gastrectomy, can lead to significant improvements in insulin sensitivity and resolution of type 2 diabetes in some cases. Regular health screenings, including blood glucose tests and assessments of insulin sensitivity, are essential for early detection and intervention in individuals at risk for insulin resistance

and related metabolic disorders. Early management of insulin resistance can help prevent or delay the onset of more severe metabolic conditions (Wu *et al*., 2019).

6. Conclusion

Insulin plays a central role in regulating glucose metabolism and maintaining metabolic balance in the human body. Its actions extend beyond glucose regulation, as it also influences protein and lipid metabolism, cellular growth, and proliferation. However, disruptions in insulin function can lead to insulin resistance, a condition characterized by reduced cellular responsiveness to insulin. Insulin resistance is a key contributor to the development of various metabolic disorders, including type 2 diabetes, cardiovascular diseases, non-alcoholic fatty liver disease (NAFLD), obesity, and polycystic ovary syndrome (PCOS). It is influenced by a combination of genetic predisposition, lifestyle factors, and environmental influences. Chronic inflammation, elevated free fatty acids, and abnormal regulation of lipolysis are among the molecular mechanisms that contribute to insulin resistance.

The consequences of insulin resistance are far-reaching, affecting multiple organ systems and increasing the risk of serious health conditions. These include type 2 diabetes, cardiovascular diseases, liver diseases, obesity-related complications, and an increased risk of certain cancers. Effective management of insulin resistance and its associated health effects requires a multifaceted approach. Lifestyle modifications, such as weight management, a balanced diet, regular physical activity, and stress reduction, play a critical role in improving insulin sensitivity. Pharmacological interventions, such as oral antidiabetic medications and targeted therapies, can also be beneficial in managing insulin resistance. In severe cases, bariatric surgery may be considered for individuals with obesity and significant insulin resistance. Early detection and intervention are essential for preventing the progression of insulin resistance to more severe metabolic disorders. Regular health screenings and a proactive approach to maintaining metabolic health are crucial in identifying insulin resistance early and implementing appropriate measures to manage it effectively. In conclusion, understanding the mechanisms of insulin action and insulin resistance provides valuable insights into the pathophysiology of metabolic disorders. By focusing on prevention, early detection, and a holistic approach to management, we can strive to improve insulin sensitivity and metabolic health, leading to better overall well-being and a reduced burden of metabolic diseases.

References

Araki, E., Lipes, M.A. , Patti, M.-E. , Brüning, J.C. , Haag Iii, B. , Johnson, R.S. , & Kahn, C. R. (1994). Alternative pathway of insulin signalling in mice with targeted disruption of the IRS-1 gene. *Nature*, 372, 186–190. https://doi.org/10.1038/372186a0.

Bedinger, D.H., Adams, S.H. (2015). Metabolic, anabolic, and mitogenic insulin responses: A tissue-specific perspective for insulin receptor activators. *Molecular and Cellular Endocrinology*, 415, 143–156. https://doi.org/10.1016/j.mce.2015.08.013.

Boucher, J., Kleinridders, A., & Kahn, C.R. (2014). Insulin receptor signaling in normal and insulin-resistant states. *Cold Spring Harbor Perspectives in Biology*, 6, a009191. https://doi.org/10.1101/cshperspect.a009191.

Cho, H., Mu, J., Kim, J.K., Thorvaldsen, J.L., Chu, Q., Crenshaw, E.B., Kaestner, K.H., Bartolomei, M.S., Shulman, G.I., & Birnbaum, M.J. (2001). Insulin resistance and a

diabetes mellitus-like syndrome in mice lacking the protein kinase Akt2 (PKBβ). *Science*, 292, 1728–1731. https://doi.org/10.1126/science.292.5522.1728.

Cho, H., Thorvaldsen, J.L., Chu, Q., Feng, F., & Birnbaum, M.J. (2001). Akt1/PKBα is required for normal growth but dispensable for maintenance of glucose homeostasis in mice. *Journal of Biological Chemistry*, 276, 38349–38352. https://doi.org/10.1074/jbc.C100462200.

Corpeleijn, E., Saris, W.H.M., & Blaak, E.E. (2009). Metabolic flexibility in the development of insulin resistance and type 2 diabetes: Effects of lifestyle. *Obesity Reviews*, 10, 178–193. https://doi.org/10.1111/j.1467-789X.2008.00544.x.

DeFronzo, R.A., Tripathy, D. (2009). Skeletal muscle insulin resistance is the primary defect in type 2 diabetes. *Diabetes Care*, 32, S157–S163. https://doi.org/10.2337/dc09-S302.

Erion, D.M., Shulman, G.I. (2010). Diacylglycerol-mediated insulin resistance. *Nature Medicine*, 16, 400–402. https://doi.org/10.1038/nm0410-400.

Gaster, M. (2007). Metabolic flexibility is conserved in diabetic myotubes. *Journal of Lipid Research*, 48, 207–217. https://doi.org/10.1194/jlr.M600319-JLR200.

Gao, X., Lowry, P.R., Zhou, X., Depry, C., Wei, Z., Wong, G.W., & Zhang, J. (2011). PI3K/Akt signaling requires spatial compartmentalization in plasma membrane microdomains. *Proceedings of the National Academy of Sciences*, 108, 14509–14514. https://doi.org/10.1073/pnas.1019386108.

Goodpaster, B.H., Sparks, L.M. (2017). Metabolic flexibility in health and disease. *Cell Metabolism*, 25, 1027–1036. https://doi.org/10.1016/j.cmet.2017.04.015.

Hausdorff, S.F., Fingar, D.C., Morioka, K., Garza, L.A., Whiteman, E.L., Summers, S.A., & Birnbaum, M.J. (1999). Identification of Wortmannin-sensitive Targets in 3T3-L1 Adipocytes: Dissociation of insulin-stimulated glucose uptake and glut4 translocation. *Journal of Biological Chemistry*, 274, 24677–24684. https://doi.org/10.1074/jbc.274.35.24677.

Hsu, P.P., Kang, S.A., Rameseder, J., Zhang, Y., Ottina, K.A., Lim, D., Peterson, T.R., Choi, Y., Gray, N.S., Yaffe, M.B., Marto, J.A., & Sabatini, D.M. (2011). The mTOR-regulated phosphoproteome reveals a mechanism of mTORC1-mediated inhibition of growth factor signaling. *Science*, 332, 1317–1322. https://doi.org/10.1126/science.1199498.

Hubbard, S.R. (2013). The insulin receptor: both a prototypical and atypical receptor tyrosine kinase. *Cold Spring Harbor Perspectives in Biology*, 5, a008946 https://doi.org/10.1101/cshperspect.a008946.

Marchesini, G., Brizi, M., Morselli-Labate, A.M., Bianchi, G., Bugianesi, E., McCullough, A.J., Forlani, G., & Melchionda, N. (1999). Association of nonalcoholic fatty liver disease with insulin resistance. *American Journal of Medicine*, 107, 450–455. https://doi.org/10.1016/S0002-9343(99)00271-5.

Mehran, A.E., Templeman, N.M., Brigidi, G.S., Lim, G.E., Chu, K.-Y., Hu, X. , Botezelli, J.D., Asadi, A., Hoffman, B.G., Kieffer, T.J., Bamji, S.X., Clee, S.M., & Johnson, J.D. (2012). Hyperinsulinemia drives diet-induced obesity independently of brain insulin production. *Cell Metabolism*, 16, 723–737. https://doi.org/10.1016/j.cmet.2012.10.019.

Morigny, P., Houssier, M., Mouisel, E., & Langin, D. (2016). Adipocyte lipolysis and insulin resistance. *Biochimie*, 125, 259–266. https://doi.org/10.1016/j.biochi.2015.10.024.

Morino, K., Petersen, K.F., & Shulman, G.I. (2006). Molecular mechanisms of insulin resistance in humans and their potential links with mitochondrial dysfunction. *Diabetes*, 55, S9–S15. https://doi.org/10.2337/db06-S002.

Muoio, D.M. (2014). Metabolic inflexibility: When mitochondrial indecision leads to metabolic gridlock. *Cell*, 159, 1253–1262. https://doi.org/10.1016/j.cell.2014.11.034.

Pederson, T.M., Kramer, D.L., & Rondinone, C.M. (2001). Serine/threonine phosphorylation of IRS-1 triggers its degradation: possible regulation by tyrosine phosphorylation. *Diabetes*, 50, 24–31. https://doi.org/10.2337/diabetes.50.1.24.

Perreault, L., Newsom, S.A., Strauss, A., Kerege, A., Kahn, D.E., Harrison, K.A., Snell-Bergeon, J.K., Nemkov, T., D'Alessandro, A., Jackman, M.R., MacLean, P.S., &

Bergman, B.C. (2018). Intracellular localization of diacylglycerols and sphingolipids influences insulin sensitivity and mitochondrial function in human skeletal muscle. *JCI Insight, 3*(3), https://doi.org/10.1172/jci.insight.96805.

Petersen, M.C., Shulman, G.I. (2018). Mechanisms of insulin action and insulin resistance. *Physiological Reviews*, 98, 2133–2223. https://doi.org/10.1152/physrev.00063.2017.

Rahimi, Y., Camporez, J.-P.-G., Petersen, M.C., Pesta, D., Perry, R.J., Jurczak, M.J., Cline, G.W., & Shulman, G.I. (2014). Genetic activation of pyruvate dehydrogenase alters oxidative substrate selection to induce skeletal muscle insulin resistance. *Proceedings of the National Academy of Sciences*, 111, 16508–16513. https://doi.org/10.1073/pnas.1419104111.

Youngren, J.F. (2007). Regulation of insulin receptor function. *Cellular and Molecular Life Sciences*, 64, 873–891. https://doi.org/10.1007/s00018-007-6359-9.

Wei, L., Hubbard, S.R., Hendrickson, W.A., & Ellis, L. (1995). Expression, characterization, and crystallization of the catalytic core of the human insulin receptor protein-tyrosine kinase domain. *Journal of Biological Chemistry*, 270, 8122–8130. https://doi.org/10.1074/jbc.270.14.8122.

White, M.F. (2012). *Mechanisms of Insulin Action in Atlas of Diabetes:* Fourth Edition, edited by Skyler J. Springer.

Wu, L., Derynck, R. (2009). Essential role of TGF-beta signaling in glucose-induced cell hypertrophy. *Developmental Cell*, 17, 35–48. https://doi.org/10.1016/j.devcel.2009.05.010