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INSULIN RESISTANCE REVIEW

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Abstract
Insulin is a vital hormone produced by the beta cells of the pancreas, which helps in regulating the amount of sugar present in the blood. Any alteration in the insulin concentration can lead to various pathological changes, such as diabetes and insulin resistance. Insulin resistance occurs when the insulin receptors in the body fail to respond to insulin, which results in the reduction of glucose uptake in cells. Although several reasons have been identified as the possible cause of insulin resistance, it is challenging to pinpoint a single cause. In this review, we will discuss the various causes of insulin resistance and some of its effects.

Keywords: insulin, insulin receptors, insulin resistance, hyperinsulinaemia, type 2 diabetes, insulin signaling pathway, adipose tissue.

Insulin

Insulin is the peptide hormone responsible for maintaining the sugar level in the bloodstream. This hormone is synthesized by the beta cells of the pancreatic islets. Insulin is composed of 51 amino acids with A and B chains, joined by disulphide bond. There are 21 amino acids in the A chain and 30 in the B chain. The B chain has a core helical segment, while the A chain has an N-terminal helix connected to an anti-parallel C-terminal helix. Two disulphide bonds, connecting the A chain's N- and C-terminal helices to the B chain's central helix, bind the two chains together. The N-terminus of the A chain and the C-terminus of the B chain of pro-insulin are connected by a connecting peptide [1]. Mature human insulin has a molecular mass of 5808 Da and the chemical formula is $C_{257}H_{383}N_{65}O_{77}S_6$. Despite its small size, this hormone possesses nearly all of the structural characteristics that are common to proteins, such as the α-helix, β-sheet, β-turn, high-order assembly, allosteric T- and R-transitions, and conformational changes in amyloidal fibrillation [2].
The structure of insulin is essential to its ability to control blood glucose levels. Insulin lowers blood glucose levels by promoting the uptake of glucose from the bloodstream into cells through binding to its receptor on target cells, which starts a signaling cascade. Insulin-related disorders, including diabetes mellitus, frequently result in changes in insulin secretion, synthesis, or receptor function, which impairs glucose metabolism.

Insulin receptors

INSR is a member of the class of receptor tyrosine kinases (RTKs), which in humans consists of 58 receptors. The cytoplasmic and extracellular (ectodomain) domains of INSR are connected by a single transmembrane helix, just like other RTKs. Members of the IR family, such as ISRR and the insulin-like growth factor-1 receptor (IGF-1R), have

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unique structural properties that set them apart from other RTKs [3]. The heterotetrameric receptor tyrosine kinase known as INSR is made up of two membrane-spanning β subunits that contain tyrosine kinase domains and two extracellular α subunits that bind insulin [4]. The α- and β-subunits are produced by proteolytic cleavage of an internal cleavage site and are connected by a disulphide bridge. The N-terminal signal peptide is eliminated through further proteolysis. A stable heterotetrameric α2β2 structure is formed by disulphide bridges connecting the two extracellular α-subunits. Each of the β-subunits has an intracellular protein tyrosine kinase and a single transmembrane domain. In order to activate the innate protein tyrosine kinase, insulin or IGFs engage with the α-subunits of INSRs or IGF1Rs, resulting in a conformational change that is conveyed through the transmembrane β-subunits [5].

It was also clear that the α and β chains were organized into multiple domains. The receptor was observed to consist of the following: three predicted fibronectin type III domains (designated FnIII-1, FnIII-2, and FnIII-3, or F1, F2, and F3), a transmembrane (TM) domain, an intracellular juxtamembrane segment (JM), a tyrosine kinase (TK) domain, and a C-terminal tail (C-tail) [6]. There are two isoforms of IRs, IR-B and IR-A. The inclusion or absence of exon 11, which causes length discrepancies between the two isoforms, distinguishes these isoforms. The distribution of these two transcript variants throughout the body, their activities, and their affinity for ligand binding are also different. When it comes to binding insulin, IR-A has a greater binding affinity. But in contrast to IR-B, it has a noticeably higher affinity for IGFs, specifically for IGF-II. Additionally, the internalization and recycling rates of IR-A are higher [7].

Insulin binding to the insulin receptor and insulin pathway

After activation, INSR undergoes autophosphorylation and enters the cell by means of endocytosis. To initiate subsequent signaling cascades, phosphorylated INSR attracts and activates target molecules such as protein phosphatases, Src homology 2-B (SH2-B), and insulin receptor substrates (IRSs). After then, INSR is controlled in the protein-sorting early endosome (EE) for later trafficking. The majority of INSRs are recycled back to the plasma membrane after being inactivated and sorted in EE, with a little percentage being translocated into the nucleus or to the late endosome for destruction [8].

In a physiological sense, the ligand activates the function of the INSR in the insulin/IGF-1-like signal (IIS) pathway. The IIS system, sometimes referred to as a major nutrient-dependent endocrine route, controls a wide range of physiological functions, including growth and development, metabolism, and more. Within the IIS pathway, the IR controls two principal cell-signaling cascades: the mitogen-activated protein kinase (MAPK) pathway (extracellular signal regulated kinase signaling pathway (ERK)) and the phosphatidylinositol-3-kinase (PI3K)/AKT signaling network. The PI3K/AKT pathway is principally in charge of regulating metabolic activities such the transfer of glucose and the creation of proteins, lipids, and glycogen. On the other hand, the MAPK

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pathway is principally accountable for cell growth and proliferation and is associated with the mitogenic effects of insulin [9].

Type 2 diabetes

The WHO first classified diabetes in 1965 using an age-related definition (such as maturity-onset), then in 1980 it adopted a therapeutic definition (such as non-insulin dependent diabetic mellitus, or NIDDM), and in 1999 it established the true categorical split of diabetes into type 1 and type 2. Type 2 diabetes is "due to a progressive loss of b-cell insulin secretion frequently on the background of insulin resistance," according to the American Diabetes Association, but at least the World Health Organization recognizes that it is "commonly associated with overweight and obesity." [10].

A complicated interaction between genetic predispositions and environmental factors leads to type 2 diabetes. Muscle and adipose tissue, the two main typical peripheral insulin-responsive tissues, show a decreased responsiveness to insulin at the outset of the disease, which results in a decreased disposal of excess circulating glucose and fatty acids. Simultaneously, hepatic gluconeogenesis rises as a result of decreased insulin action on the liver, hence aggravating hyperglycemia. The pancreatic beta cell makes up for this during the early stages of the illness by secreting more insulin. Nevertheless, increased beta-cell dysfunction is also seen during this compensatory hyperinsulinemia period that precedes the development of overt diabetes, highlighting the fact that Type 2 diabetes is dependent on insults that occur at both the peripheral and beta-cell levels [11]. The primary pathophysiological event leading to the development of type 2 diabetes, aside from β cell failure, is the target tissues' resistance to insulin, which is typically linked to aberrant insulin production. Clinically speaking, the phrase "insulin resistance" suggests that maintaining normoglycemia requires higher-than-normal insulin concentrations. Cellularly speaking, it describes the insufficient potency of insulin signaling from the insulin receptor to the ultimate insulin action substrates that are implicated in many metabolic and mitogenic facets of cellular activity [12].

Insulin resistance

The concept of insulin resistance originated from Himsworth's observations, wherein he observed that when insulin and glucose were injected simultaneously into diabetic individuals, one of two outcomes was observed. Insulin-sensitive diabetics were those whose blood glucose remained steady or even dropped in response to the challenge. Others who had a significant rise in blood glucose were deemed insulin-insensitive [13]. Insulin resistance can arise due to a combination of acquired and hereditary causes. Mutations and polymorphisms of insulin receptors, glucose transporters, and signaling proteins involved in insulin signal transduction are among the prevalent genetic abnormalities. Obesity, physical inactivity, advanced glycation end products (AGE), excess free fatty acids (FFAs), psychological stress, smoking, alcohol consumption, or certain drugs are among the acquired reasons of insulin resistance. These are all associated with persistent low-grade inflammatory disorders [14].

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Increased insulin requirements result from insulin resistance's partial reduction of the liver's glucose production and poor insulin-mediated glucose absorption in the periphery (skeletal muscle and adipose tissue). Hyperglycemia occurs when higher insulin needs are not met by increasing insulin levels. In healthy individuals, skeletal muscle accounts for about 80% of glucose uptake during a hyperinsulinaemic euglycemic clamp. Insulin resistance is the state in which an attenuated biological response is produced by a normal or increased insulin level. Insulin resistance reduces muscle's ability to absorb glucose. When combined with the liver's inability to control glucose production, this leads to hyperglycemia and hyperlipidemia, which are two of the co-morbidities linked to insulin resistance and type 2 diabetes (T2D) [15]. Damaged myocardial insulin signaling, mitochondrial dysfunction, endoplasmic reticulum stress, altered calcium homeostasis, irregular coronary microcirculation, dysfunction of the sympathetic nervous system, renin-angiotensin-aldosterone system initiation, and abnormalities in the immune response are the hallmarks of the hyperinsulinemic state. Increased oxidative stress, fibrosis, hypertrophy, diastolic cardiac dysfunction, and ultimately systolic heart failure are the outcomes of these pathophysiological changes, and it has been proposed that hyperinsulinemia is the shared factor responsible for the link between obesity and type 2 diabetes. Typically, fasting glucose levels are used to determine the reference range for hyperinsulinemia, which includes 5–13 μU/mL, ≤30 μU/mL, and 18–173 pmol/L (3–28 μU/mL) REF. Two common conditions of insulin resistance include obesity and type 2 diabetes. Insulin resistance controls insulin secretion, which eventually results in hyperinsulinemia. In patients with obesity, hyperinsulinemia is linked to higher morbidity and mortality from cardiovascular problems. Insulin resistance is typically the primary cause of hyperinsulinemia, a condition for which the pancreas produces extra insulin in order to compensate [16]. It is also recognized that insulin resistance is linked to other diseases like dyslipidemia, hypertension, and central obesity. The metabolic syndrome refers to the grouping of several disorders in metabolism. One known risk factor for the emergence of insulin resistance and the metabolic syndrome is obesity. Apart from the overall fat mass, the location of adipose tissue is also crucial, with visceral depots being the site of greater insulin resistance. Extensive research is being conducted to determine the mechanisms by which the anatomic distribution and accumulation of adipose tissue may be linked to the development of insulin resistance [17].

Numerous routes can contribute to the development of insulin resistance in obese individuals. Several studies have indicated that proinflammatory cytokines and endoplasmic stress activate the serine kinases I kappa B kinase (IKK-b) and c-Jun N-terminal kinase (JNK), which phosphorylate IRS1 at serine sites (serine 302 pS302 and serine 307 pS307). Meanwhile, this can set off biological reactions that result in insulin resistance. Obesity, persistent inflammation, and metabolic illnesses like type 2 diabetes are frequently linked to these conditions [18]. Moreover, the receptor itself may be involved in some types of insulin resistance. Many phenotypes of insulin resistance may be explained by changes in the expression, binding, phosphorylation state, and/or

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kinase activity of the insulin receptor. Furthermore, it's likely that specific insulin activities are selectively inhibited by the targeted inhibition of particular phosphorylation sites [19].

Ectopic lipid buildup in peripheral tissues—particularly in the liver and skeletal muscle—has been linked to more severe insulin resistance even in the absence of visceral adiposity, obesity remains a clear and substantial risk factor for type 2 diabetes. Non-alcoholic fatty liver disease (NAFLD) is consistently identified in over 70% of obese persons with T2DM, and patients with NAFLD nearly always have both T2DM and hepatic insulin resistance. Furthermore, in individuals with T2DM, NAFLD, and lipodystrophic conditions, therapies that lower intrahepatic triglyceride level by slight weight reduction or leptin therapy significantly restore hepatic insulin resistance. Compared to visceral adipose tissue volume, intrahepatic and intramyocellular lipid contents are thought to be far better indicators of insulin resistance, which suggests that increased lipid accumulation in the liver and skeletal muscle may impede insulin signaling and lead to insulin resistance [20].

Mitochondria in insulin resistance

Mitochondria is important for the insulin signaling of tissues that rely on insulin. Insulin not only keeps the NAD/NADH ratio in mitochondria constant and dampens down the activity of forkhead box O (FOXO) 11/heme oxygenase (HMOX) 12, but it also forms the cornerstone of the integrity of the mitochondrial electron transport chain (mETC). Oxidative stress impairs insulin signal transduction and dysregulates adipokines, which leads to insulin resistance. Furthermore, it plays a role in the activation of many serine-threonine kinase pathways, including JNK and inhibitor of nuclear factor kappa-B kinase subunit beta (IKKβ)/NF-κB. These processes ultimately result in the phosphorylation of insulin receptor substrate (IRS) proteins and the subsequent breakdown of IRS. Elevated free radical levels inhibit insulin signaling, which in turn suppresses the cell membrane GLUT-4 localization [21]. Several investigations on both humans and animals have established a link between type 2 diabetes and lowered oxidative capabilities. Reduced oxidative phosphorylation ability per mitochondria or a decrease in mitochondrial bulk have been linked in several studies to impaired mitochondrial oxidative capacity. It is still up for debate, though, whether or not mitochondrial malfunction is the main factor causing insulin resistance. It has been observed that in the initial phases of obesity and insulin resistance, there is an increase in lipid β-oxidation instead of a decrease in β-oxidation. Besides, there is an increase in insulin action rather than a decrease due to mitochondrial insufficiency and poor fat burning. These findings imply that insulin resistance is not caused by skeletal muscle mitochondrial deficiencies [22].

Genetic mutations and insulin resistance

A decrease in the number of mature INSRs available or the affinity of INSR for insulin binding can result from mutations affecting the α subunit of INSR. In addition,

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alterations pertaining to the β subunit tyrosine kinase domain may hinder autophosphorylation, hence influencing the subsequent signaling cascades' activation. Donohue syndrome, Rabson-Mendenhall syndrome, and type A insulin resistance syndrome are among the few recessively inherited illnesses for which genetic reasons of insulin resistance have been identified. These causes stem from mutations in the INSR gene [23]. Insulin resistance and other metabolic syndromes are linked to mutations in the insulin receptor (IR) gene, and these conditions can result in T2D cardiovascular diseases. There are about 50 IR mutations known to be connected to uncommon types of insulin resistance. It is rare, though, for T2D to be brought on by a persistent insulin resistance mutation resulting from IR mutation. The main cause of insulin resistance is irregularities in the transduction of the insulin signal [24].

Aging in insulin resistance

Human aging is linked to the emergence of age-related diseases such as hyperglycemia and insulin resistance. It is commonly recognized that type 2 diabetes and glucose intolerance become more common as people age. Nevertheless, little is known about the mechanism behind age-related insulin resistance [25]. According to damage theories, one of the main causes of aging is the buildup of ROS, which causes accumulative damage to lipid, protein, and DNA molecules. Oxidative stress is caused by damage to enzymes and accumulation of metabolites. As a result, it increases the non-canonical metabolic activity of cells and may be involved in pathology and age-related disorders. Lipid peroxidation products accumulate as a result of oxidative damage, which results in the loss of cell membrane characteristics. Additionally, senescence is associated with a lower frequency of age-related pancreatic beta cell malfunction and peripheral insulin sensitivity [26].

Adipose tissue in insulin resistance

Since a greater knowledge of the fundamental biological processes of this organ has emerged in recent decades, the significance of adipose tissue in maintaining whole-body metabolic homeostasis has come to light. It was always thought that adipose tissue just functioned as a store of inert energy, but several research has shown that it also functions as a significant endocrine organ that secretes chemokines, cytokines, and adipokines [27]. White adipose tissue (WAT) and brown adipose tissue (BAT) are the names for the two distinct forms of well-differentiated adipose tissue found in humans, each with a distinct distribution and function. The main function of the WAT is related to the storage of excess energy as triacylglycerol, or fat, which has the capacity to expand and can be mobilized through hormonal signaling. The storage of excess fat is linked to mechanical overload and a slow to moderate increase in the risk of metabolic disorders. The enhanced expression of fatty acid synthase (FAS) and glycerol-2-phosphate dehydrogenase, as well as transporters of glucose sensitive to insulin (GLUT4), are characteristics of mature WAT. In contrast, BAT plays a role in energy expenditure and body weight regulation through thermogenesis processes [28].

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Many chemicals with diverse activities are secreted by adipose tissues. These compounds include proteins (adipocytokines), which have autocrine, paracrine, or endocrine effects on a variety of metabolic processes, and free fatty acids (FFA), which have well-documented pathophysiological effects on glucose homeostasis. Adipokines are involved in the development of insulin resistance. They modify the insulin sensitivity of the target organs (liver, muscle) either locally or systemically, with the effects being mediated by immunological, neuroendocrine, and autonomous pathways. Furthermore, the stromal cells found in adipose tissues play a role in the metabolism of glucocorticoids and sex hormones, which has an impact on adipogenesis, the metabolism of carbohydrates and fats, and cardiovascular processes [29].

In addition, extra calories are stored as adipose or ectopic lipid in vascular cells, myocytes, hepatocytes, and β-cells when nutrition intake surpasses energy expenditure. This might result in the production of harmful metabolites including ceramides and Diacylglycerol (DAG). Consequently, Protein kinase C (PKC) isoforms that support insulin resistance may become activated. Accumulation of excess nutrients can negatively impact the adipocyte itself, resulting in events that might negatively impact the body. These events include increased expression of GCSF (granulocyte colony-stimulating factor), leptin, IL-6, and IL-8. Proinflammatory M1-macrophages are drawn to these and other cytokines, and they release factors like TNFα that can cause both localized and systemic inflammation and insulin resistance [30].

Acylation-stimulating protein

Acylation-stimulating protein (ASP), which is produced by the interaction of complement C3, factor B, and adipsin, is released in significant quantities by adipose tissue. In order to promote triglyceride accumulation in adipose cells, ASP increases fatty-acid re-esterification and glucose transport. Obese individuals have higher plasma ASP levels, and resistance to ASP may cause fatty acid to be channeled specifically into the liver. Because there is less triglyceride storage in the adipose tissue of ASP-deficient organism, there is a moderate reduction in the bulk of adipose tissue and an increase in sensitivity to insulin [31].

Resistin

Numerous circulating hormones and cytokines, including resistin, leptin, and tumor necrosis factor alpha (TNF-α), are produced by adipocytes and function as systemic signals that alter peripheral tissues' insulin signaling pathways and energy consumption [32]. The pathogenic significance of resistin has been a subject of contention due to the only 59% homology between human and mouse resistin. This limitation also affects the comparability of human disease and animal models. According to preliminary research in mouse models, resistin gets its name from its capacity to "resist," or obstruct, the action of insulin. This is supported by the results of a preliminary investigation that found that recombinant resistin given to healthy mice increases insulin resistance, that neutralizing antibodies can block the action of resistin and improve insulin sensitivity, and that diet-induced obesity in mice results in elevated plasma resistin levels. Resistin has been demonstrated to correlate with insulin resistance in both humans and rats,

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supporting the hypothesis that it plays a significant role in regulating insulin resistance in the context of obesity. These preliminary research have led to this conclusion. In research, people and obese animal models have higher plasma resistin levels, which in turn drop as a person loses weight. On the other hand, other research has revealed that resistin generated from adipose tissue is decreased in obesity, sparking the ongoing debate about resistin's function in obesity. There is evidence that circulating resistin levels are primarily influenced by visceral fat, which lends credence to the idea that resistin and insulin resistance are related [33].

Conclusion

In addition to the aforementioned objective factors, certain changeable lifestyle factors—such as stress, sleep, smoking, food, and exercise—are also thought to play a role in insulin resistance. For example, there is a link between increased risk for obesity and IR and irregular daily eating patterns or poor sleep. Furthermore, the disruption of circadian clocks may potentially play a significant role in the development of IR through a number of mechanisms, such as clock gene mutations, irregular sleep cycles, shift work, and jet lag. What is more, epidemiologic studies conducted by various institutions have demonstrated that people who engage in regular exercise, maintain a healthy diet that includes more soluble fiber, colorful fruit and vegetables, green tea, or less intake of added sugars, carbohydrates, or trans fats, limit their alcohol intake, abstain from smoking, and experience lower levels of stress do, in fact, increase their sensitivity to insulin [34].

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