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Unraveling Insulin's Mechanisms: A Comprehensive Analysis

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Abstract. Insulin, a peptide hormone synthesized and secreted by pancreatic β-cells, exerts a wide range of anabolic effects on multiple tissues. It plays a crucial role in maintaining complete-frame gas homeostasis by promoting carbohydrate, fat, and amino acid uptake and storage in skeletal muscle, adipose tissue, and the liver. Insulin stimulates glucose transportation and storage as glycogen in skeletal muscle, while simultaneously inhibiting glycogenolysis and gluconeogenesis in the liver. In adipocytes, it enhances glucose uptake, glycerol synthesis, and triglyceride formation while suppressing lipolysis. During fasting periods, decreased circulating insulin levels and increased secretion of counter-regulatory hormones lead to the breakdown of stored fuels, providing metabolic substrates for cellular energy. The dynamic changes in insulin levels during feeding and fasting states play a key role in fuel metabolism and blood glucose regulation. Additionally, insulin influences protein catabolism, translation, cell growth, differentiation, and survival through mitogenic and anti-apoptotic processes, resulting in a net synergistic effect on various biological pathways.

Keywords. Insulin receptors, insulin movement, insulin receptor substrate, pleckstrin homology domain, protein tyrosine phosphatase.

1. Introduction

Insulin target cells express a variety of unique effector systems that are primarily responsible for mediating the cell- and organ-specific biological functions of insulin. Effector systems include rate-limiting enzymes, enzymatic pathways, membrane transport systems, gene expression, processes regulating cellular trafficking of proteins and vesicles, and systems governing translation, post-translational modification, and protein degradation. Certain aspects of linear insulin signal transduction are evolutionarily conserved; however, complex patterns of interaction between the signal and evolved effector systems are more pronounced in mammals and allow for greater plasticity in adaptive responses [1].

This study first discusses insulin signaling pathways and networks that are common to multiple target cell types. Recent advances in our understanding of the cell processes and pathways that inhibit insulin signaling have been delineated. Subsequently, Unique aspects of insulin action are described, in particular key effector systems, which are properties of skeletal muscle, adipocytes, and liver, and explain the distinct effects on biological functions in these tissues. Finally, nutrient-sensing pathways and cell stress responses are discussed in terms of their interaction with insulin signaling and their role in the pathogenesis of insulin resistance. Insulin action: proximal signaling pathways Proximal steps in insulin signaling, including the insulin receptor, insulin receptor substrate proteins (IRS), lysophosphatidylinositol 3 (PI 3) kinase, Akt/protein kinase B (Akt/PKB), and mitogen-activated protein kinase (MAPK), are globally operative in multiple cell types. These proteins also serve as points of divergence or nodes in an expanding matrix of signal transduction pathways and are highly regulated, both positively and negatively, via cross-talk with other signaling systems and modulatory pathways (Figure 1).

2. Insulin receptor molecules

Insulin action is initiated by its specific binding to high-affinity receptors on the plasma membrane of target cells and is a large transmembrane glycoprotein consisting of two α - and two β-subunits that form a heterotetramer. The insulin receptor is synthesized from a single gene that consists of 22 exons and 21 introns. Following the translation of its mRNA, it is processed into two separate subunits (α and β) that assemble as a disulfide-linked holo enzyme with (αβ) 2 histochemistry [2]. The 135 KDA α - subunits, derived from the amino-terminal portion of the pro receptor, reside entirely on the outside of the cell, tethered to the membrane via the 95 KDA β - subunits that span the membrane. Insulin binds to the extracellular α- subunits. This binding results in conformational changes that bring the α - subunits closer together, and enable ATP to bind to the intracellular domain of the β-subunit, leading to autophosphorylation of distinct tyrosine residues on the β-subunit. Auto phosphorylation augments the intrinsic activity of the β-subunit as a tyrosine kinase, directed against other tyrosines within the receptor, as well as tyrosine phosphorylation of exogenous substrates. Ligand-dependent stimulation of β-subunit tyrosine kinase activity is critical for the promulgation of insulin signaling. At least six tyrosine residues in the β - subunit undergo phosphorylation and have been shown to serve different roles in insulin signaling. These are within the three functional groups. Phosphorylation of Tyr 972 establishes a recognition motif and docking site that provides sufficient stability to the receptor–substrate complex for intracellular substrate phosphorylation. Tyrosine phosphorylation sites at positions Tyr 1158, Tyr 1162, and Tyr 1163 are essential for mediating increases in subunit tyrosine kinase activity and signal transduction. Phosphorylation sites Tyr 1328 and Tyr 1334 affect the sensitivity of Ras/MAPK pathway activation and are thus involved in the receptor mitogenic responses [3].

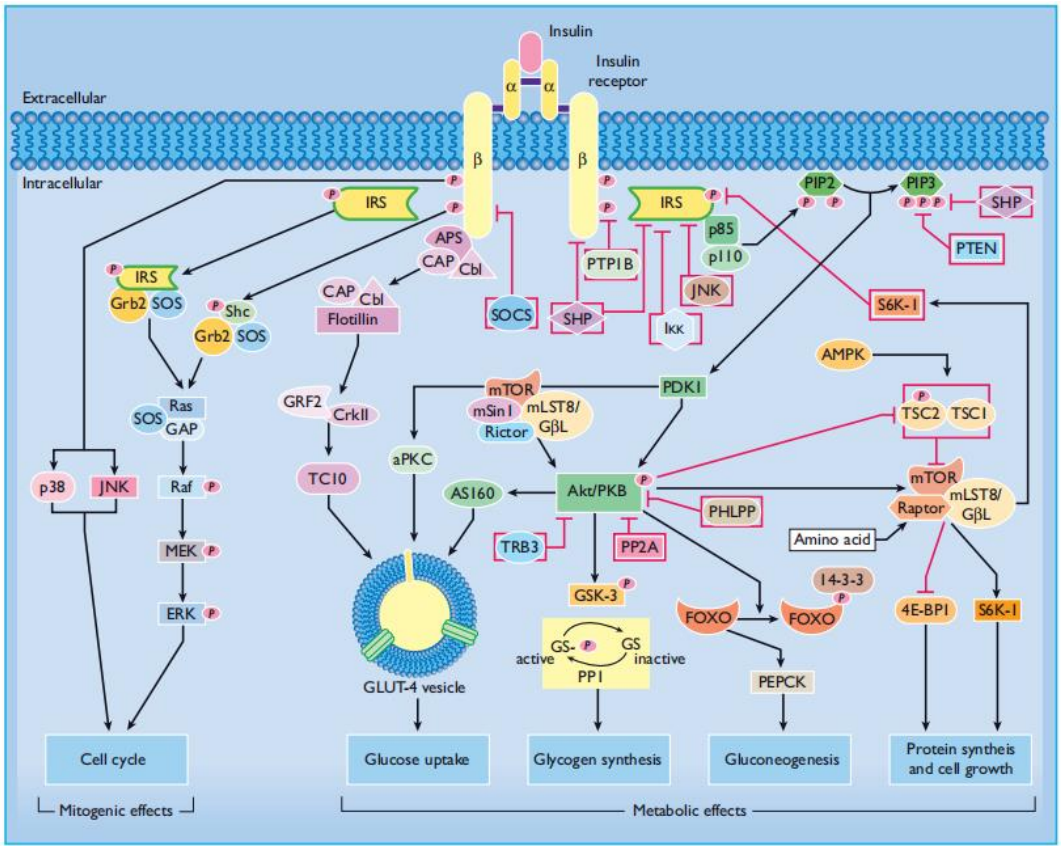

Figure 1. A schematic illustration of insulin signaling pathways involved in both metabolic and mitogenic effects. Arrows represent an activation process; blocked arrows represent an inhibition process

The number of cell-surface insulin receptors is downregulated by chronic exposure to high insulin concentrations in vitro, and receptor loss has been observed in target cells from Hyperinsulinemic insulin-resistant humans. Receptor loss can impair maximal insulin responsiveness. This is illustrated by genetic ablation of the insulin receptor in mice, which results in lethality 4 – 5 days after birth because of severe diabetic ketoacidosis [4]. Insulin-stimulated glucose uptake and activation of glycogen synthase in muscles are severely impaired in muscle-specific insulin receptor knockout mice [5]. These latter animals also have features of the metabolic syndrome including increases in fat mass, serum triglycerides, and serum free fatty acids, but retain normal basal and contraction-stimulated glucose transport systems [6]. Transgenic mice expressing dominant-negative insulin receptors also develop obesity, hyperinsulinemia, glucose intolerance, and hypertriglyceridemia. These phenotypes were analogous to those observed in insulin-resistant humans. Patients with genetic mutations in the insulin receptor gene (type B insulin resistance) or circulating antibodies directed against the insulin receptor that blocks ligand binding (type A insulin resistance) develop severe insulin resistance, acanthosis Nigricans, and glucose intolerance. In addition to receptor downregulation, the intrinsic activity of the insulin receptor tyrosine kinase is impaired in insulin-resistant humans and patients with type 2 diabetes mellitus (T2DM) via several regulatory and pathophysiological processes described in this chapter. The number and functional activity of the insulin receptors are critical for effective insulin activity.

The insulin receptor is similar in structure to the insulin-like increase component 1 receptor (IGF1R) and several growth factors and cytokine receptors which have an extracellular ligand-binding domain that turns on an intracellular tyrosine kinase area. The mammalian insulin-like signaling gadget consists of three nicely-described ligands: insulin, insulin-like growth thing 1 (IGF - 1), and insulin-like boom issue 2 (IGF - 2), All three ligands can bind and prompt cellular-surface insulin receptors [7]. alternative splicing concerning exon eleven of the insulin receptor

The gene determines the insertion or deletion of 12 amino acids near the COOH terminus of the α- subunit. Isoform A lack 12 amino acids and has an excessive affinity for IGF-2, which predominates throughout fetal development and promotes growth due to IGF-2 binding. Isoform B, which includes 12 amino acids, predominates postnatally and is especially activated with the aid of insulin. a few pieces of evidence support the contention that dysregulated expression of the fetal sample can occur in grownup tissues and bring about insulin resistance [8].

2.1. Insulin receptor substrate molecules

Following insulin binding and receptor autophosphorylation, the following committed step in signal transduction is the tyrosine phosphorylation of intracellular proteins. at least 11 intracellular substrates have been diagnosed which can be unexpectedly phosphorylated on tyrosine residues by way of ligand-bound insulin receptors, consisting of six insulin receptor substrate (IRS) proteins, Grb2 - related binder 1 (Gab1), Cas Br M (murine) esotropic retroviral remodeling sequence homolog (Cbl), and numerous isoforms of Src - homology - 2 - containing protein (Shc) [9]. IRSs are instant

substrates for insulin receptor tyrosine kinase and are of fundamental importance for insulin motion. IRS proteins have an N terminal pleckstrin homology (PH) domain, a phosphatases-binding (PTB) domain, and a COOH-terminus vicinity of variable duration containing multiple tyrosine and serine phosphorylation websites [10]. The PH area allows the position IRS for coupling with the insulin receptor, probable through binding to the charged head companies of sure phosphatidylinositides in adjoining membrane systems. PTB domain names recognize phosphotyrosine inside the amino acid collection asparagine-proline–any amino acid-phosphotyrosine (NPXpY), which encompasses Tyr 972 within the juxta membrane area of the insulin receptor β-subunit and helps the formation of the IRS – insulin receptor complex. The middle and C - terminus of IRS proteins incorporate up to twenty capability tyrosine phosphorylation websites that, after phosphorylation using the insulin receptor, bind to other intracellular molecules that comprise Src - homology - 2 domain names (SH2 domain names). The SH2 - containing proteins that bind to passerine–threonine serine-threonine kinases and protein tyrosine phosphatases, inclusive of PTP1B and SHP2, as defined under [15]. similarly, IRS1 can be post-translationally modified through either O - linked N - acetyl glucosamine adducts (O-GlcNAc) on serine – threonine residues beneath hyperglycemic conditions [16] or S-nitrosylation on account of nitric oxide technology [17]. those adjustments set off the proteasomal down law of IRS1 and insulin resistance.

2.2. PI3 Kinase

Among the many proteins that bind to IRS1/2, PI3 kinase is important for regulating insulin metabolic events and signaling, which promotes glucose uptake in skeletal muscle and adipose tissue. Three related kinases represent a relative circle of enzymes that phosphorylate the hydroxyl group in the inositol ring of the membrane phosphatidyl inositol (Pt-dins) [18]. PI signal (three, four, five) P3 propagates insulin signaling; hence, the decision I subset of PI3K is responsible for the action of receptor tyrosine kinases (including insulin receptors) and Ras/MAPK [19]. Class I PI 3kinase is a hetero dimeric molecule composed of regulatory subunits and catalytic subunits. There are currently five putative regulatory subunits, specifically p85 α, p55 α, p50 α, p85 β, or p55 γ (collectively known as p85 subunits), and one of these regulatory subunits is associated with catalytic subunits. One of four known p110s, p110 α, p110 β, p110 δ or p110 γ [20]. Under normal conditions, the number is lower, and there are more than p85 regulatory subunits compared to the thep85-p110complex number, which may be a negative regulator of insulin motility. The stoichiometry of interaction with the immobilized p85 and p85-p110 complex is clarified as it can compete with the p85–p110 complex for recruitment of immobilized p85 to the "free" IRS phosphotyrosine-docking 4454 sites (i. [21] Long-term expression of p85 can lead to insulin resistance, as seen in gestational diabetes or serious complications in which expression of p85 in skeletal muscle is ameliorated.p85 subunit can also be negatively activated by the action-talk-stress- kinase pathway. Recent research suggests that p85 is required for insulin-stimulated activation of c-Jun NH2-terminal kinase (JNK), which occurs in states of insulin resistance, to combine with high-fat foods to cause weight problems and JNK. overexpression [22]. As the JNK pathway inhibits insulin motility, the involvement of p85 in JNK activation provides a mechanism for transduction – crosstalk between the PI 3-kinase signaling pathway and JNK--mediated stress or inflammatory responses. In addition, p85 can inhibit insulin by upregulating phosphatase and tensin homolog (PTEN), a phosphoinositide phosphatase that disrupts PI (3, 4, 5) P3 and inhibits downstream insulin signaling [23]. Tris-phosphoinositide-D-dependent p-protein kinase 1 Insulin-mediated activation of PI tri-kinase leads to phosphorylation of the inositol ring to form PI in the 3' function of phosphatidyl inositol in membrane glycolipids, 3. This leads to the recruitment of signaling proteins with PH domains to the plasma membrane. Membrane-bound-interacts with phosphoinositide to activate each activated protein and activates them in downstream signals. 3-Phosphoinositide-producing protein kinase 1 (PDK1) binds to PI (3,4,5) P3 and is responsible for the downregulation of Akt/PKB and aPKC. PDK1 ameliorates the degradation of these kinases by phosphorylating the Akt/PKB activation loop at Thr 308 and also ζ at Through 410. Enhancing the activity of these kinases.

2.3. Akt/Protein Kinase B

Phosphorylation and activation of Akt/PKB are mediated by various insulins and augment cellular responses by these factors, including promotion of GLUT-quadruple translocation to the plasma membrane, inhibition of glycogen synthase kinase III (GSK-3). induces triglyceride synthesis by increasing the expression of sterol regulatory element-binding protein 1c (SREBP-1c) and supports cell survival by inhibiting apoptosis. Akt/PKB is a multi-substrate serine-threonine kinase, including cyclin-based total kinase inhibitor p21kip, GSK3β, Bcl-2 cell loss antagonist, AS160-side, endothelial NO synthase, fork presence kinase, signaling protein, and transcriptional elements. area O1 class (Foxo 1), etc. In mammals, there are three Akt/PKB isoforms, each encoded by a specific gene (Akt1, Akt2, and Akt3). Aktl and Ak2 are widely distributed. However, Akt2 is essential for insulin-sensitive tissues, including the liver and adipose tissue. Akt3 is expressed in tensors and testis. Various data link Akt/PKB to various natural processes mediated by glucose transport stimulation and insulin. Expression of the combined Akt/PKB gene affects the translocation of GLUT-4 to the plasma membrane of muscle cells and adipocytes [24]. Loss of Akt1 leads to growth retardation and reduced lifespan without metabolic disruption [25]. When analyzed, Akt2-deficient mice exhibit insulin resistance and persistent diabetes because insulin stimulates glucose utilization and is unable to reduce glucose uptake in the liver [26]. Mechanistic studies report that Akt2 is an altered isoform of GLUT (with a 4-fold increase in glucose levels). PKB activation is associated with many insulin responses. One of the first substrates identified for Akt/PKB was GSK3β. Phosphorylation of GSK3β prolongs glycogen synthesis by reducing glycogen synthase activity [28] Proteins activating

Rab-GTPase (pores) 29] under basal conditions, the useful architectural domain of AS160 is required to maintain the Subcellular localization of GLUT-4 [30]. When stimulated with insulin, phosphorylation of AS160 closes the follicle and shifts the balance of the target Rab to the GTP- associated, active form, allowing GLUT-4 to be retained in the body, enabling GLUT-4 translocation [30]. As expected, this effect was reversed upon pretreatment with the PI3 kinase inhibitor wortmannin, indicating that the signaling occurs through PI3 kinase. This AS160 expression response affects skeletal muscle in patients with insulin resistance.

2.4. Atypical protein kinase C

Protein kinase C isoforms are categorized aAS160 is impaired in skeletal muscles collected from insulin-resistant patients. conventional (α, β, γ) (cPKC), novel (δ, θ, ε, η, μ) (nPKC), and atypical (ζ, λ) (aPKC), depending on their ability to be activated by calcium and diacylglycerol (DAG). cPKCs and nPKCs frequently act as negative feedback inhibitors of insulin receptors and IRS, as discussed below. aPKCs are involved in signal transduction and, similar to Akt/PKB, are activated by the PI 3 kinase pathway, which helps regulate insulin metabolism. The two aPKC isozymes ζ and λ differ in their tissue-specific expression and different animal species; for example, PKC λ is the dominant aPKC in rat bone marrow and adipose tissue, whereas PKC ζ is expressed in rats, while it is dominant in monkeys. and people. Activation of PKC ζ and PKC λ occurs in the vicinity of Akt/PKB due to direct interaction with 3' phosphoinositide and/or phosphorylation, and activation of PDK1.aPKCs have been shown to play a role in insulin-stimulated glucose uptake and GLUT-4 translocation in adipocytes and muscle [31]. Stimulation of glucose transport and GLUT-4 vesicle translocation by aPKC may be due to its effect on the actin cytoskeleton, as PKCλ/ζ can affect Rac and actin dynamics [32]. Overexpression of active forms of PKCζ and PKCλ increases, expression of negative forms of aPKCs decreases, and glucose transporter activity and exchange of GLUT-4 decreases in response to insulin (31). Decreased levels of aPKC have been reported in the muscles of humans with T2DM and mice with insulin resistance [33]. Convincingly, mouse models with muscle-selective deletion of PKC lambda showed insulin resistance, resulting in insulin-resistant muscle glucose and reduced GLUT-4 translocation. The mechanism by which aPKC is involved in metabolic signaling has not yet been fully elucidated. The CAP/Cbl/TC10 pathway was compared to the PI 3-kinase pathway, and substantial evidence confirmed that the CAP/Cbl/TC10 pathway is involved in promoting glucose transport [34]. Differential pathways at the insulin receptor kinase level mediate tyrosine phosphorylation of the Cbl proto-oncogene by a mechanism that does not involve IRS. This step of phosphorylation requires recruitment of the adapter protein APS containing the SH2 and PH domains to the insulin receptor β-subunit and extension of CBL to APS [35]. APS interacts with phosphotyrosine in the insulin receptor activation loop, with the name SH2. Upon receptor binding, APS is phosphorylated on C-terminal tyrosine, allowing Cbl to be recruited to APS at the SH2 domain of Cbl, followed by phosphorylation of Cbl at tyrosine. Cbl-associated protein (CAP) is also incorporated together with Cbl into the insulin receptor-APS complex via tandem SH3 domains at the COOH-end of CAP binding to the proline-rich domain in Cbl. CAP also has a sorbin homology (SoHo) domain in its NH2-terminal region. After dissociation of CAP/Cbl from insulin, the CAP SoHo domain binds to flotillin in caveolin-containing lipid rafts in the plasma. Lipid rafts are areas of the plasma membrane rich in cholesterol, glycolipids, and sphingolipids, which control problems caused by the accumulation of specific protein components.

Once the CAP/Cbl complex binds to flotillin, tyrosine-phosphorylated Cbl provides a recognition site for the recruitment of CrkII to the C3G complex into lipid rafts. CrkII binds to the specific phosphorylation site of CBL via the SH2 domain and associates with the nucleotide exchange of C3G produced via the SH3 domain. C3G is a guanylate of TC10 and other low-molecular-weight GTP-binding proteins. TC10, a member of the Rho family of GTPases, targets the lipid raft domain because of its ability to be modified via farnesylation and palmitoylation. Conversion of the Rab protein between GTP- and GDP-dependent states affects vesicle budding from the donor membrane and fusion with the acceptor membrane.TC10 is known to regulate the actin cytoskeleton [36]. Downstream effectors of TC10, which are thought to be involved in the transcription of GLUT-4, have been identified [37].

2.5. Ras - p38 MAPK pathway

Signal differences from IRS Junction proteins Another aspect of the difference is the inclusion of the Ras/MAPK signal pathway, which has an important role in parent cell growth and mitosis. One of the SH2 domain-containing proteins that bind to IRS after insulin-mediated tyrosine phosphorylation of IRS is Grb-2, a small cytoplasmic adapter protein. Grb-2 also has an SH3 binding domain, one of which binds proteins with a proline-rich sequence, one of which is the animal homolog protein of Drosophila (SOS), the GDP/GTP exchange factor. This interaction localizes the SOS to enable the Ras/MAPK pathway. Membranes activated by SOS-supported GTP bind the 21 kDa low-molecular-weight GTPase and GTP-bound form of the Ras complex and activate Raf-1 kinase. Raf-1 kinase then initiates a cascade that leads to phosphorylation, synthesis, and activation of the dual-specific kinase MEK (MAPK/ERK kinase), which phosphorylates residues of threonine and Tyrosine Kinases (ERK21). Activated ERK phosphorylates multiple targets, mediating the mitogenic effects of the Ras/MAPK pathway and the growth-promoting effects of insulin [38]. Insulin can also modulate the activity of the Ras/MAPK pathway through the insertion of another substrate molecule, SHC. Independent of IRS, SHC forms a complex with Grb-2/SOS, activating the Ras/ Raf-1/MEK phosphorylation cascade in response to insulin. Whether activated by IRS or SHC, ERK1/2 translocates into the nucleus and phosphorylates transcription factors such as ELK-1, thereby modulating DNA-binding properties and gene

transcriptional regulation. ERK can also phosphorylate p90 ribosomal protein S6 kinase (p90 S6 kinase) and regulate the activity of components, such as c-fos. In addition, the MAPK cascade promotes glycogen synthase because p90 S6 kinase can activate glycogen-associated protein phosphatase-1, which dephosphorylates and activates glycogen synthase [39]. Thus, the MAPK pathway can interact with metabolic processes. However, the MAPK pathway is not required to promote glucose transport and is not thought to be associated with the metabolic effects of insulin [40]

Inhibition of Insulin Signal Transduction propagates the insulin signaling pathway; however, many mechanisms block this signal. These inhibitory mechanisms may represent a normal function of insulin activity when the organism is undergoing a physiological change or may cause a pathophysiological phenomenon and the development of insulin resistance when insufficient. Disclosure of the inhibitory mechanism provided insight into the wider network of insulin regulatory pathways and identified therapeutic targets because blocking this inhibitory mechanism can increase insulin sensitivity. Inhibition of the insulin receptor, which is the most important factor in insulin signaling, also has many mechanisms that can reduce the effect of insulin at the insulin receptor level. For example, it has long been known that prolonged insulin stimulation causes loss of cell surface insulin receptors and that this downregulation problem impairs insulin sensitivity. Additionally, various cellular proteins and processes can modulate the tyrosine kinase activity of insulin. Both strategies (serine-threonine phosphorylation and protein tyrosine phosphatase) affect both insulin receptors and IRS insert molecule.

Downregulation of insulin receptor number continual publicity of high insulin levels results in the lack of insulin receptors, ensuing in an insulin reaction curve (e.g., decreased insulin sensitivity). That is due to ligand-mediated accelerated internalization of insulin receptors, followed by way of lysosomal degradation, and reduced gene expression. Insulin stimulation results in the phosphorylation of Foxo1, which disrupts its interplay with the insulin receptor promoter and reduces insulin receptor gene transcription, leading to the lack of the receptor and insulin resistance [41]

Plasma differentiation factor 1 (PC-1), also known as exonucleoside nucleotide pyrophosphatase phosphodiesterase 1, is a membrane glycoprotein with pyrophosphatase activity and acts as an insulin inhibitor. PC-1 binds to amino acids 485–599 of the insulin receptor-binding site, a site required for translocation of the receptor β-subunit, and allows autophosphorylation after insulin binding. The interaction with PC-1 involves positions close to the two β-subunits required for trans phosphorylation. PC-1 muscle expression was increased in diabetic and obese subjects and was associated with decreased muscle mass. insulin receptor tyrosine phosphorylation and muscle glucose uptake. Analysis of PC-1 gene polymorphisms in a variety of individuals and family cohorts suggests that alterations in this gene are associated with the risk for the development of childhood and adult obesity, as well as T2DM [43].

Grab proteins

Growth factor receptor-bound proteins (Grb proteins) constitute a family of structurally related multi-domain adapters with diverse cellular functions but lack intrinsic enzymatic activity. Grb10 and Grb14 can bind to phosphotyrosine residues on the insulin receptor and alter the receptor tyrosine kinase activity [44].

Overexpression of Grb10 and Grb14 in cells inhibits insulin-stimulated phosphorylation of IRS1, IRS2, and Shc [45]. However, the physiologic role of Grb proteins is not fully clear, and their actions may be tissue-specific, with capabilities as an inhibitory factor or a positive mediator in the insulin signaling pathway Inhibition of insulin receptor substrate proteins. Protein phosphotyrosine phosphatases Endogenous protein phosphotyrosine phosphatases (PTPase scan-dephosphorylates tyrosine residues on the insulin receptor β - subunit and insulin receptor substrate docking molecules, resulting in a dampening of insulin signal transduction. Two PTPases in particular, PTP - 1B and leukocyte common antigen-related phosphatase (LAR) contribute to insulin receptor dephosphorylation in insulin target cells [46]. Membrane-associated PTPase activity is increased in the skeletal muscle of patients with T2DM [47], principally because of increments in cytosolic PTPase - 1B and membrane-associated LAR [48]. The ability of PTPases to modulate insulin signaling has been demonstrated in mice with genetic ablation of PTPase - 1B, which exhibits enhanced insulin sensitivity, increased insulin-mediated tyrosine phosphorylation of the receptor and IRS1, and failure to develop insulin resistance when fed a high-fat diet [46]. Muscle-specific overexpression of PTP-1 B in mice induces tissue insulin resistance with decreased capacity for insulin receptor Autophosphorylation [49]. Thus, the available data consistently demonstrate that PTPase -1B can negatively modulate insulin signaling through the dephosphorylation of tyrosine residues in the insulin receptor and IRSs. However, the role of LAR in insulin receptor function remains poorly understood.

Serine–threonine phosphorylation

Serine–threonine phosphorylation of insulin receptors and IRS docking proteins is a major mechanism for the negative modulation of insulin signal transduction. Serine phosphorylation diminishes insulin receptor tyrosine kinase activity and decreases receptor – IRS coupling by inhibiting the insulin-mediated tyrosine phosphorylation of IRS - 1, binding and activation of PI 3 kinase, and stimulation of glucose transport. Consensus sequences in IRS - 1 make it susceptible to a wide variety of serine–threonine kinases, including PKC, PKA, Akt/PKB, MAPK, S6 kinase, GSK3, casein kinase II, Cdc2 kinase, JNK, and IκB kinase ÷ (IKK β). Several of these kinases have been shown to function as Physiological modulators and cause desensitization of insulin signaling pathways under conditions of nutrient excess, inflammation, and cell stress responses. For example, JNK and IKK β are activated by inflammatory stimuli (for

example TNF α) contributing to insulin resistance, and PKC is activated by DAG which accumulates with increased availability of free fatty acids.

Protein kinase C

PKCsareserine–threonine kinases with multiple substrates, including IRS docking proteins and the insulin receptor [50]. Serine–threonine phosphorylation of IRS impairs its ability to associate with the insulin receptor and with PI 3 kinase, resulting in the desensitization of the PI 3-kinase pathway. Hyperinsulinemia, hyperglycemia, and elevated circulating free fatty acids (e.g. nutrient excess) lead to increased intracellular DAG, which in turn activates conventional and novel PKC isoforms principally via recruitment to the plasma membrane. These conditions are associated with increased serine–threonine phosphorylation and diminished insulin receptor and IRS protein function. In addition, insulin activates atypical PKCs, such as PKC ζ, via the PI 3 kinase pathway, which is also capable of phosphorylating and Desensitizing IRS [51].

Tumor necrosis factor α

Tumor necrosis aspect α (TNF-α) is a cytokine produced by using a manner of immune cells, adipocytes, and muscle agencies. while having little impact on systemic circulating concentrations, TNF - α expression is increased in adipose and muscle tissues as a feature of insulin resistance [52]. In adipose tissue, TNF-α and different seasoned-inflammatory cytokines are produced by using the use of adipocytes and macrophages that infiltrate adipose tissue underneath conditions of obesity and insulin resistance. This increases the possibility that cytokines can bring about cell insulin resistance through autocrine and/or paracrine consequences. TNF-α induces serine phosphorylation of IRS1, thereby lowering its ability to be phosphorylated with the aid of the usage of insulin receptor tyrosine kinase and impairing downstream insulin sign transduction [53]. several pathways activated by way of TNF - α are implicated in elevated serine phosphorylation of IRS - 1, including the pressure-added about kinases, JNK and IKK β.

JNK

Three JNK-encoding genes have been described in mammals; JNK1 and JNK2 are ubiquitously expressed, whereas JNK3 expression is restricted to neuronal tissues. JNK isoforms belong to the extended family of MAPKs and control many cellular functions through the regulation of activator protein 1 (AP - 1). In addition to TNF - α signaling, insulin also activates JNK1 and JNK2 [54], which then display increased serine kinase activity against multiple intracellular substrates including IRS1, IRS2 and Shc. The ability of insulin to activate JNK represents a negative feedback mechanism by which insulin inhibits its signaling; JNK activity is also increased during cellular responses such as endoplasmic reticulum stress and is increased under conditions of insulin resistance. Descriptive data included the observation that a high-fat diet- increases Ser 307 phosphorylation of IRS1 in wild-type mice, but not in JNK1-/- mice, which are characterized by reduced adiposity, increased insulin receptor signaling, and improved insulin sensitivity. gets. [55]. JNK has been implicated in the pathogenesis of metabolic syndrome and insulin resistance in T2DM. NF-KB activates JNK--mediated pathways and inhibits insulin signaling by increasing serine phosphorylation of IRS1 [56]. NF-κB is a transcription factor that acts as a "master switch" () during inflammation, upregulating the expression of various inflammatory mediators. NF-κB is usually retained in the cytoplasm by binding to members of the κB (IκB) inhibitor family. During inflammation or metabolic stress, NF-κB is activated by the IκB kinase (IKK) complex, which is composed of two catalytic subunits, IKKa and IKKβ, and a regulatory subunit, IKKγ. The IKK β subunit phosphorylates IκB,causing its ubiquitination, followed by proteasomal degradation and release of NF-κB.Free NF-kB can then translocate to the core and activate the transcription of at least125 genes, most of which are proinflammatory [57]. Comprehensive information is available regarding the role of NF-kB in the IR pathogenesis of insulin resistance.Activation of NF-κB by a high-fat diet, obesity, and insulin resistance in metabolic syndrome. Proinflammatory cytokines such as TNF-α and interleukin 6 (IL-6) canactivate NF-κB. Circulating monocyte cells in obese patients showed increased transcription of pro-inflammatory genes regulated by NF-kB, with reduced IκB.Weight loss, calorie restriction, and exercise reduced the expression of NF-κB [58] regulated genes. Anti-inflammatory drugs, such as thiazolidinedione, statins, and salicylates, can inhibit the secretion of cytokines by interfering with the NF-pathway IκB Kinase-β IKK β is a serine kinase that desensitizes insulin signaling via serine phosphorylation of the IRS or insulin receptor. The desensitization of TNF-α can be mediated in elements by using IKK β due to the serine phosphorylation of IRS. regular with this hypothesis, heterozygous ablation of the IKK β gene prevents insulin resistance in mice fed an excessive-fats food regimen or overweight leptin-deficient ob/ob mice [59, 60]. mice (LIKK mice), mice expressing IKKβ activity selectively in hepatocytes exhibited a T2DM phenotype characterized by means of hyperglycemia, excessive insulin resistance, and mild insulin resistance, together with in muscle [56]. The hepatic manufacturing of proinflammatory cytokines, including IL-6, IL-1β, and TNF-α, accelerated to similar degrees in LIKK mice.

The identical phenomenon takes place whilst wild rats consume fats. but, muscle-unique IKK β- knockout mice showed no difference in weight problems brought about by insulin resistance compared to wild-kind mice [61] and skeletal muscle. the primary feature of salicylate is to inhibit IKK β [62]. Predictably, salicylate subsequently reduced IKK JNK--mediated serine phosphorylation of IRS, thereby enhancing insulin sensitivity. remedy with high doses of salicylate improves glucose tolerance and insulin sensitivity in humans and rats [59]. Accelerated catabolism of PI

(3,4,5) P 3 by phosphoinositide phosphatases. Increased PI (3,4,5) P 3 production due to active PI 3 kinase is key to metabolic insulin signaling and downstream K1 activation. PTEN can phosphorylate PI (3,4,5) P3 at position 3 and SH2-containing inositol phosphatases (SHIPs) phosphorylate PI (3,4,5) at position 5 of the inositol ring. In both cases, the ability of PI (3,4,5) P3 to stimulate PDK1 is lost. Thus, PTEN and SHIP may modulate the adverse effects of insulin, particularly the metabolic effects of [63]. Although many studies support the hypothesis that PTEN may be involved in the dysregulation of insulin activity in pathophysiological diseases, its role in human insulin resistance is yet to be determined.

Inhibits insulin signaling through protein-protein interactions

Inhibitor of cytokine signaling 3 The SOCS protein family (CIS and SOCS 1-7) was Initially identified as a negative feedback loop for cytokine receptors, including Janus kinase (JaK). Ligand activation of cytokines and growth receptors phosphorylates JaK and activates signal transducers and activators of transcription (STATs). The phosphorylated STAT family, homodimers, or heterodimers form four homodimers. 4, where they act as transcriptional activators. STAT improves SOCS gene expression in the nucleus. SOCS proteins then resupply to inhibit tyrosine-phosphorylated cytokine receptors, prevent phosphorylation of cytokine receptor substrates by competition from SH2 domains, or inhibit JaK tyrosine kinases with a role in binding and. Evidence suggests that it may act on insulin via a similar mechanism [46]. Studies have shown that SOCS-1, SOCS-3, and SOCS-6 can block the interaction between insulin receptors and IRS by binding to the COOH-terminus of the β-subunit of insulin receptors [64]. Interestingly, several factors that induce insulin resistance in cells also induce SOCS-3 expression, including TNF-α, growth hormone, and leptin.

Tribbles

The mammalian tribble (TRB) family consists of three proteins, with and without a kinase domain. Accordingly, TRBs are “pseudo kinases” that lack detectable kinase activity but can bind to kinase substrates in phosphorylation cascades and inhibit their phosphorylation. For example, TRB proteins can bind to Akt/PKB and inhibit its phosphorylation and activation in response to insulin, [65] whereas down-regulation of TRB3 improves insulin sensitivity [66].

Tissue-specific insulin action: the role of insulin effector systems

Insulin regulates whole-body fuel homeostasis via specific effects on multiple target tissues. The nature of these biological actions varies dramatically from tissue to tissue, and these variations, for the most part, are not caused by differences in insulin signal transmission (described above). Rather, tissue-specific. The effects of insulin are principally explained by the effector systems that are uniquely expressed in a variety of differentiated target cells. The biochemical basis of these effects is described in skeletal muscle, adipose tissue, and the liver, three organs that are primarily responsible for fuel storage and oxidation, as well as counter-regulatory metabolism.

Skeletal muscle Insulin-induced glucose transport

Skeletal muscle is responsible for most insulin-stimulated glucose in the body, andthe main effect of insulin on tissue is in its basic structure to support the glucose transport effector system (Fig. 7.2). Transporter proteins (GLUTs) facilitate the transport of glucose in the plasma, and 13 members of the GLUT/SLC2 family have been identified. All GLUT proteins are tightly packed in the membrane, and the most conserved area is the chamber, which has a pore-forming function that facilitates monosaccharides expansion. Each glucose transporter isoform plays a different role in glucose metabolism based on tissue expression patterns, substrate specificity and affinity, transport kinetics, and expression regulation under different physiological conditions. The main transporter subtypes that regulate glucose transport in insulin-resistant diabetes are GLUT-1 and GLUT-4. In inactive cells, GLUT-1 controls the cell and promotes the release of glucose into the cytosol, where it crosses the plasma membrane and is rapidly phosphorylated and metabolized by hexokinases. As >90%of the cellular content of GLUT-4 is initially in the intracellular tissue, GLUT-4contributes minimally to glucose transport in unstimulated cells. Insulin improves blood glucose levels via the plasma membrane uptake of intracellular GLUT-4, the rate-limiting rate-limiting insulin-stimulated glucose uptake and metabolism in peripheral tissues. Impairment of glucose transport after cessation of insulin signaling is a result of intracellular GLUT-4 transporters. Later, GLUT-4 is the major transporter mediating insulin-stimulated glucose transport activity in tissues, such as skeletal and cardiac Muscle and adipose tissues. In unstimulated muscle or adipose cells, a component of GLUT-4 resides in an inducible tubular-vesicular storage compartment that includes the trans-Golgi network and endosomal vesicles located near the endo facial surface of the plasma membrane. However, another component of cellular GLUT-4 exists in active endocytosis–endosomal recycling pathway that cycles GLUT - 4 between endosomes and the plasma membrane. The recycling pathway results in the localization of approximately 4 – 10% of GLUT - 4 in the basal plasma membrane, and this steady-state distribution is the balance of rapid endocytosis and slow recycling. Insulin shifts the distribution of GLUT - 4 from intracellular pools towards the plasma membrane, both by elevating the exocytotic rate of GLUT - 4 in the recycling pathway and by recruiting GLUT-4 from the inducible storage compartment to the cell surface. Deactivation of transport is accomplished via A slowing of the

exocytotic rate and an acceleration of the endo-cytotoxic rate, as GLUT - 4 is retrieved from the plasma membrane through clarinet-dependent and - independent mechanisms [67,68].

GLUT-4 vesicle trafficking involves actin and the microtubules cytoskeleton. Insulin stimulates cytoskeletal rearrangement, with the appearance of cortical β- actin fiber projections that subtend the plasma membrane. This actin remodeling is under the control of small G-proteins of the Rho, Rab, and Rac families. Microtubules surround the inducible intracellular depot of GLUT - 4andmicrotubulee proteins such as dynein and kinesin have been co-purified with GLUT - 4. Inhibition of actin remodeling or disruption of microtubules using depolymerizing agents inhibits GLUT - 4 translocation and stimulates glucose transport. Data suggest that the exocytotic movement of GLUT - 4 begins with its transfer to actin scaffolds that connect the microtubules-cytoskeleton with the plasma membrane, which positions GLUT - 4 vesicles for docking and membrane fusion.

The complete pathway linking insulin signal transduction to stimulation of the glucose transport system has not been fully elucidated. Activation of transport is critically dependent on insulin-mediated autophosphorylation of insulin receptors, Tyrosine phosphorylation of IRS1 and activation of PI 3 kinase. PI(3,4,5)P 3 by PI 3 kinase activates PDK1. At this point, PDK1 activates two separate kinase pathways that contribute to GLUT - 4 translocations and stimulation of glucose transport activity: Akt2 and atypical PKCs (PKC ζ and PKC λ). Akt2 then phosphorylates and inhibits AS160 (TBC1D4) and TBC1D1 [69], which are Rab GTPase-activating proteins. The modulation of AS160 activates Rab small GTPases that in turn regulate aspects of GLUT - 4 vesicle docking and cytoskeletal organization [70]. Simultaneously, the ligand-bound insulin receptor activates the CAP/Cbl/TC10 pathway upstream of IRS1 phosphorylation and activates TC10, a Rho family member that regulates the actin cytoskeleton. Importantly, the factors that link TC10, AS160, atypical PKCs, and other relevant factors with the glucose transport effector system, which impels complex changes in GLUT - 4 vesicle trafficking associated with transporter translocation, are unknown. Muscle contraction: stimulation of glucose transport independent of insulin signaling.

Muscle contraction results in GLUT - 4 translocation and stimulates muscle glucose transport [71]. This effect occurs without any change in the serum insulin concentration and does not activate insulin receptors, PI3 kinase, or Akt/PKB. The mobilization of GLUT - 4 to the cell surface by acute exercise involves a different intracellular pool of GLUT - 4 from that recruited by insulin, and the effects of acute exercise and insulin are partially additive. These observations indicate that signaling systems mediating glucose transport stimulation differ in response to acute exercise versus insulin [72].

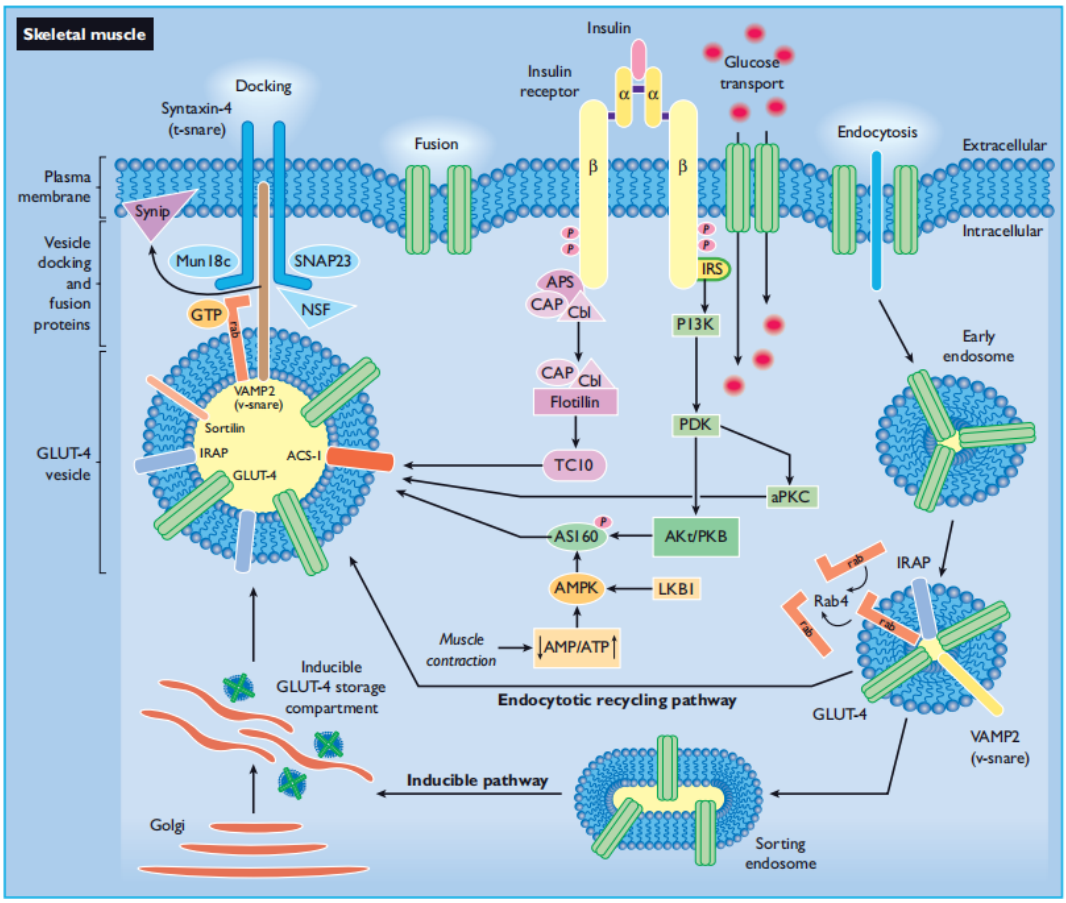

Figure 2. An overview of insulin signaling pathways in skeletal muscle. Arrows represent an activation process

This is underscored by the finding that in muscles from insulin-resistant humans and rodents, GLUT-4 translocation is impaired in response to insulin, but normal in response to acute exercise.

While signal transduction mechanisms are not fully understood, this response appears to be at least partially dependent on increments in intracellular 5 ′ AMP and the subsequent activation of adenosine 5 ′ monophosphate-activated protein kinase (. AMPK is a serine-threonine kinase that responds to fluctuations in cellular energy levels and functions to maintain energy homeostasis. When ATP levels are low and 5 ′ AMP is elevated, AMPK activates pathways for ATP regeneration and limits further ATP utilization by modifying the activity of multiple metabolic enzymes, including acetyl-CoA carboxylase (ACC), hydroxyethyl glutaryl-CoA reductase, creatine kinase, and hormone-sensitive lipase. Exercise, ischemia, and hypoxia activate AMPK via increases in AMP: ATP and creatine: phosphocreatine ratios. AMPK can also be activated through allosteric modifications and α- subunit phosphorylation by one or more upstream kinases, including LKB1.

Adipose tissue

Adipose tissue is the predominant site for fuel storage, as triglyceride and effector systems are responsible for the anabolic effects of insulin on lipogenesis, and anti-lipolysis is a key aspect of adipocyte biology (Figure 3).

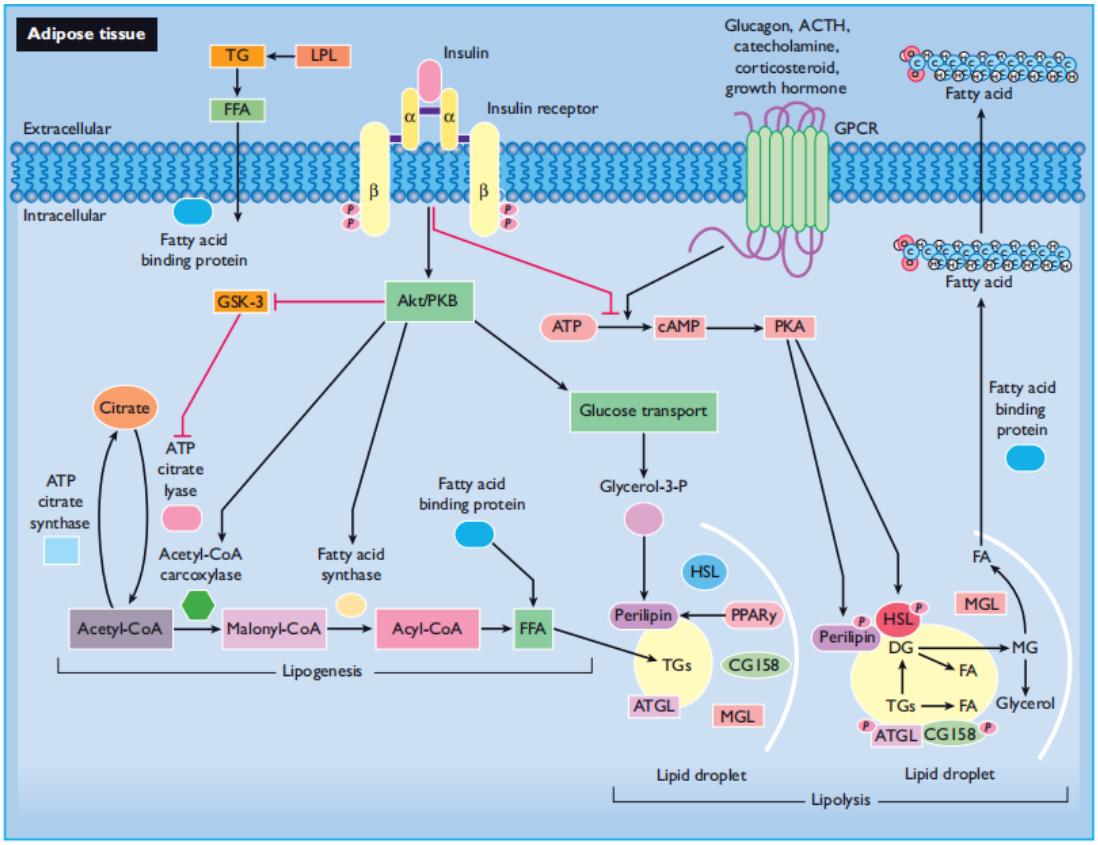

Figure 3. Summary of insulin function involved in lipogeneis and lipolysis in adipose tissue. Arrows represent an activation process; blocked arrows represent an inhibition process

Lipogenesis

Fat accumulation in adipocytes is determined by using the stability of triglyceride synthesis (fatty acid uptake and lipogenesis) and its breakdown (lipolysis/fatty acid oxidation). Insulin is an important stimulator of lipogenesis. Insulin augments the supply of each glycerol and fatty acids for triglyceride synthesis by way of growing the uptake of glucose in adipose cells, as well as activation of lipogenic and glycolytic enzymes. these enzymes represent the effector device for the biological outcomes of insulin on lipogenesis and are modulated with the aid of insulin through submit-translational changes and alteration of gene expression. regarding the publish-translational outcomes, insulin activates Akt/PKB through phosphorylation, and its role in lipogenesis is illustrated with the aid of the observation that constitutively active Akt affects excessive levels of lipogenesis in 3T3 - L1 adipocytes. Substrates for activated Akt/PKB consist of the phosphorylation and inhibition of GSK3, and this, in turn, abrogates GSK3 inhibition of ATP citrate lyase; the ensuing increase in ATP citrate, lyase hobby complements the conversion of citrate to acetyl - CoA within the cytosol. Acetyl - CoA is then to be had as the “building block” for fatty acid synthesis. Insulin also induces the gene expression of two key lipogenic proteins, fatty acid synthase (FAS) and SREBP - 1. FAS is the relevant enzyme that participates in de novo lipogenesis and catalyzes the conversion of malonyl-CoA and acetyl-CoA to long-chain fatty acids. regulation of FAS activity via insulin takes place mainly at the gene transcription stage. SREBP - 1 belongs to the elegance C bHLH (helix–loop–helix (bHLH) transcription element circle of relatives based totally on its ability to bind to the sterol regulatory element (SRE) of the low-density lipoprotein receptor gene promoter. It activates

several genes concerned with the uptake and synthesis of fatty acids and triacylglycerides. SREBP-1c is under transcriptional control through insulin [74], and overexpression of SREBP-1c mimics the effect of insulin on the expression of FAS. SREBP - 1 additionally regulates FAS expression as evidenced by using the failure of FAS and different lipogenic enzyme genes to be prompted by fasting/refeeding in SREBP - 1c–/–mice [75].

Lipolysis and anti-lipolysis

Lipolysis in adipose tissue is tightly regulated to ensure that the partitioning of metabolic fuels, glucose, and free fatty acids (FFA) is adapted to energy needs. During fasting, lipolysis is enhanced to make available FFAs that are the main oxidative fuel for the liver, the heart, and skeletal muscle, and are metabolized by the liver to ketones that replace glucose as the principal fuel for the nervous tissue. Upon feeding, lipolysis is abated, and adipocytes are converted to triglyceride storage. The rise (after a meal) and fall (with fasting) of insulin have a central role in this regulatory process as a result of its anti-lipolytic action on adipocytes. Lipolysis in normal subjects is extremely sensitive to inhibition by insulin, such that half-maximal suppression of lipolysis occurs at insulin concentrations well below those needed for the significant stimulation of glucose uptake by skeletal muscle. Higher concentrations of insulin can reduce adipocyte release of FFA to nearly zero, although at high insulin concentrations, there will still be some glycerol and FFA from the stimulatory effect of insulin on lipoprotein lipase, which acts on triglycerides in circulating lipoproteins.

Hormones regulate lipolysis in adipocytes via a coordinated action involving two major effector systems: hormone-sensitive lipase (HSL) and perilipins localized to the surface of lipid droplets. Lipolytic and anti-lipolytic (i.e. insulin) hormones exert opposite effects on HSL and perilipins by determining cAMP availability and protein kinase A (PKA) activity. Catecholamines induce lipolysis and release FFAs from adipocytes by binding to β- adrenergic receptors coupled with heterotrimeric G-proteins to adenylate cyclase, which increases cAMP production and activates PKA. The two main targets of PKA phosphorylation are HSL and perilipins [76]. The ability of insulin to antagonize hormone-induced lipolysis is largely accounted for by its ability to lower cAMP levels, thereby reducing PKA activity. The decrease in cAMP levels is mainly the result of insulin-mediated phosphorylation and activation of phosphodiesterase 3 B (PDE3B) via Akt/PKB. HSL is a key enzyme for the mobilization of triglycerides deposited in adipose tissue following activation by cAMP/PKA-dependent phosphorylation [77]. HSL is an enzyme with three isoforms ranging from 84 to 130 KDA, yet all isoforms have three domains, a catalytic Domain, a regulatory area with numerous serine phosphorylation websites required for activation, and an N - terminal variable area involved in protein and protein-lipid interactions [78]. HSL in muscles also can be stimulated by using adrenaline via β - adrenergic activation of PKA, or via muscle contraction via phosphorylation using percent at least in part activated via the ERK pathway.

Perilipins are localized at the floor of the lipid droplet in adipocytes [79] and are important within the law of triglyceride deposition and mobilization. within the absence of lipolytic stimulation, perilipins inhibit lipolysis by way of acting as a barrier in opposition to hydrolysis of the triacylglycerol by using lipases. when PKA is activated, perilipins turn into phosphorylated and translocate away from the lipid droplet, which lets in HSL to hydrolyze the lipid droplet triglyceride center [80]. Insulin blocks lipolysis by way of inhibiting PKA - mediated phosphorylation of HSL and perilipins, for this reason lowering each HSL hobby and its access to triglycerides inside the lipid droplet. In adipocytes, there are two varieties of perilipin, line with perilipin A and perilipin B, with perilipin present at a higher awareness. Adipocyte perilipin content material has an inverse correlation with lipolytic charges and an effective correlation with plasma glycerol in human beings and is reduced in overweight women. Perilipin knockout mice are lean with accelerated basal lipolysis and are proof against food regimen-caused weight problems; however, these mice increase glucose intolerance and insulin resistance greater without problems, probably because of expanded levels of serum FFAs [81]. further, perilipin has a peroxisome proliferator-activated receptor γ (PPAR γ) responsive element in its promoter region and is precipitated by using thiazolidinedione agonists of PPARY [82].

Liver

Insulin regulates hepatic metabolism through acute post-translational modifications of enzymes, together with phosphorylation, and through changes in gene expression. The stimulation of glycogen formation and gluconeogenesis using insulin are important determinants of hepatic glucose output. In Additionally, because the regulation of gene transcription is essential for the biological consequences of insulin on hepatic metabolism, mechanisms pertinent to transcriptional regulation are mentioned (Figure 4).

Glycogenesis/ glycogenolysis

Insulin exerts dramatic effects on intracellular glucose metabolism pathways Under insulin stimulation, the most important part of the glucose uptake is stored as glycogen. Insulin promotes glycogen synthesis in muscle, adipocytes, and liver with the aid of activating glycogen synthase, which adds activated glycosyl groups to developing polysaccharide chains and thus catalyzes.

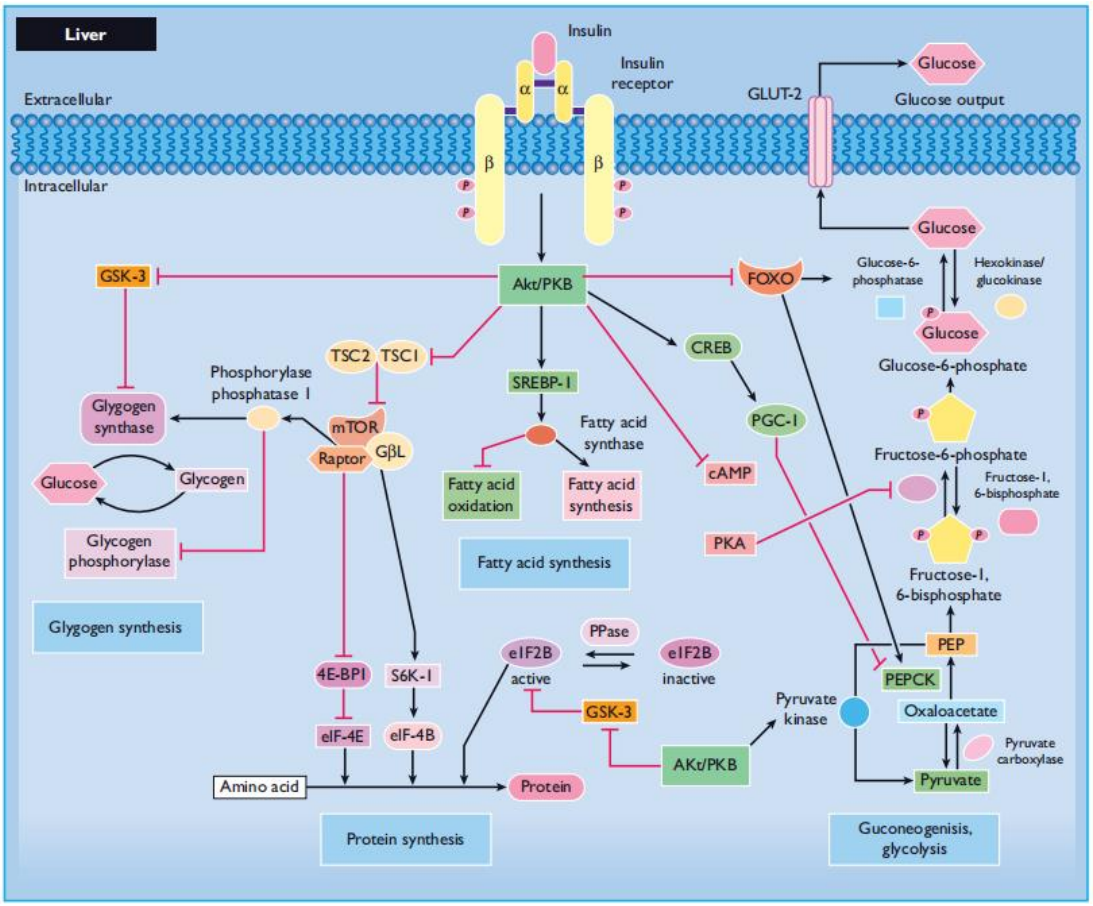

Figure 4. Summary of insulin signaling pathways in the liver that are involed in glycogen synthesis, gluconeogenesis and glycolysis, and protein synthesis, respectively. Arrows represent an activation process; blocked arrows represent an inhibition process

The final step is glycogen synthesis. Glycogen synthase regulation is complex. It involves allosteric activators, translocation of glycogen synthase to the plasma membrane in the presence of glucose metabolites and insulin [83], inhibition with the aid of phosphorylation of serine residues via unique kinases, and activation by dephosphorylation by serine-threonine phosphatases such as protein phosphatase 1 (PP1). The ability of insulin to stimulate glycogen synthase requires proximal signaling through the activation of PI 3 kinase and Akt/PKB. A downstream pathway that activates glycogen synthase involves Akt/PKB-mediated phosphorylation and inactivation of GSK3, which results in a reduction in the net phosphorylation of glycogen synthase. Reduction in glycogen synthase phosphorylation augments its activity. GSK3 β Inhibition is not the only mechanism by which insulin stimulates glycogen accumulation. In 3T3 - L1 adipocytes, insulin is capable of stimulating glycogen synthase even under experimental conditions when GSK3 β is either not detectable or present in very low amounts. Moreover, lithium, a GSK3 β inhibitor, is added to insulin to activate glycogen synthesis and glycogen synthase activity [84]. These studies indicate the existence of additional pathways for glycogen synthase activation. Inhibition of g gluconeogenesis and hepatic g glucose output Hepatic glucose production is stimulated under fasting conditions by the counter-regulatory hormones glucagon, catecholamines, and glucocorticoids, which augment glucose output by promoting glycogenolysis and gluconeogenesis. During feeding and in response to exogenous insulin injections, hepatic glucose output is potently suppressed by insulin because of the inhibition of glycogenolysis and gluconeogenesis. Gluconeogenesis is predominantly regulated through changes in gene expression of two key enzymes, phosphoenolpyruvate carboxykinase (PEPCK) and glucose - 6 - phosphatase (G - 6 - Pase). PEPCK catalyzes one of the rate-limiting steps of gluconeogenesis, whereas G - 6 - Pase catalyzes the final step, producing free glucose for transport from the liver via GLUT - 2 glucose transporters. Gene transcription of PEPCK is tightly regulated by cAMP; counter-regulatory hormones increase cAMP and induce PEPCK expression, whereas both are suppressed by insulin. In addition to the direct hormonal effects on hepatocytes, hepatic glucose output is modulated by the delivery of gluconeogenic substrates to the liver, such as lactate, amino acids, and FFA. For example, a reduction in FFA availability contributes to the suppression of hepatic glucose output by insulin through its anti-lipolytic action in adipocytes, and insulin minimizes the counter-regulatory effects of glucagon by inhibiting its secretion from pancreatic α cells. Increased hepatic glucose production is an important determinant of fasting hyperglycemia in diabetes, and has been given greater focus because of the potential importance of regulatory pathways controlling hepatic glucose output as targets of drug therapy.

General Considerations about Gene Regulation by Insulin elements within the law of liver metabolism are complex and need to be honestly elucidated. Foxo Transcription Factors The mammalian Foxo family itself consists of three expressed genes, Foxo1, Foxo3, and Foxo4, although Foxo1 is the most highly expressed isoform in insulin-responsive tissues that include liver, adipose tissue, and pancreatic β-cells. Foxo proteins contain a winged helix motif containing a

DNA binding domain. Under basal conditions, Foxo resides in the nucleus and actively regulates gene transcription. Upon insulin stimulation, Akt/PKB phosphorylates the Foxo cognate ring on three specific conserved serine and threonine residues (Thr 24, Ser 253, and Ser 319 in Foxo1). This is observed through the dissociation of Foxo proteins from DNA binding. Excluded from site and core [87]. nuclear exclusion.

The 14-3-3 protein appears to involve binding to the phosphorylated site of the Akt/PKB Foxo network and has a nuclear localization function [88]. Foxo translocation out of the nucleus is an efficient mechanism by which insulin represses the transcription hobby. The dependence of this effect on Akt/PKB phosphorylation suggests alternatives to Through 24 or Ser 253. Alanine lost phosphorylation, Foxo1 nuclear export,and failure of insulin-mediated promoter suppression [89].

The G - 6 - Pase and PEPCK promoters contain IREs that mediate transcriptional activation by Foxo1 and Foxo3 in the liver. Phosphorylation of Foxo by Akt/PKB impairs Foxo binding to this cis-element, resulting in the nuclear exclusion of Foxo and suppression of G - 6 - Pase and PEPCK gene expression. Foxo is not involved in the regulation of all the genes suppressed by insulin; however, it cannot fully account for the suppression of G - 6 - Pase and PEPCK. Under physiological conditions, there is strong evidence that SREBP - 1, LXR, and peroxisome proliferation-activated receptor-gamma 1 (PGC - 1) all contribute to the regulation of gluconeogenic genes by insulin [90]. The importance of Foxo transcription factors in cell differentiation related to whole-body metabolic homeostasis is increasingly being recognized. Foxo1 is involved in pancreatic β- cell proliferation and regulation of pancreatic-duodenal homeobox 1 (Pdx1) expression by insulin [91]. Foxo1 appears to contribute to the complex coordination of transcriptional events involved in adipocyte differentiation. Constitutively active Foxo1 prevents the differentiation of pre-adipocytes, whereas dominant-negative Foxo1 restores adipocyte differentiation of fibroblast from insulin receptor-deficient mice [92]. The binding of Foxo to its co-activator, PGC - 1 α, is disrupted by the phosphorylation of Foxo, and disruption of this complex can suppress its effects on gene transcription [93].

Sterol response e element b binding p protein 1c The SREBP family of transcription factors is classically considered to be involved in the regulation of genes in response to cholesterol availability; however, SREBP - 1c is regulated primarily by insulin [92]. This protein is also involved in adipocyte differentiation, which explains its alternative designation as adipocyte determination and differentiation factor 1 (ADD1). SREBP - 1c/ADD1 is most highly expressed in the liver, white adipose tissue, muscle, adrenal gland, and brain. Insulin stimulates transcription, post-translational processing, and nuclear translocation of SREBP - 1c in cell lines adipose, liver, and muscle tissues. In the nucleus, SREBP - 1c contributes to a positive auto-feedback loop where SREBP - 1 augments its transcription in response to insulin, involving a coordinated interaction of multiple transcription factors, including LXR α, Sp1, and SREBP - 1c itself [94]. This insulin effect is mediated through PI 3 kinase and Akt/PKB, although downstream targets and transcription factors mediating the induction of SREBP - 1c gene transcription have not been fully clarified. In addition, insulin signal transduction via the Ras/MAPK pathway plays a contributory role by increasing SREBP - 1c expression independent of changes in its mRNA levels [94]. Although multiple mechanisms may contribute to the stimulation of SREBP - 1 activity, once in the nucleus, SREBP - 1c plays an important role in the regulation of specific genes in response to insulin.

Insulin suppresses gluconeogenesis and PEPCK expression, in part through SREBP - 1c. In experiments involving overexpression of wild-type, constitutively active, and dominant interfering mutants, SREBP - 1c has also been shown to be involved in the induction of FAS and leptin in adipose cells and glucose kinase, pyruvate kinase, FAS, and acetyl-CoA carboxylase in the liver [95]. While these insulin-regulated genes contain SREs in their promoter regions, multiple hormones, metabolic substrates, and transcription factors participate in transcriptional regulation. Thus, SREBP - 1c mediates a positive transcriptional effect on genes promoting glycolysis and lipogenesis, while suppressing genes involved in gluconeogenesis, and seems to prepare the liver for carbohydrate availability following a meal. Excessive and persistent SREBP - 1c action has been implicated in hepatocellular lipid accumulation and hepatic steatosis.

Liver X receptors

Liver X receptors (LXRs) are ligand-activated nuclear receptors that regulate the genes involved in lipid and carbohydrate metabolism. Endogenous agonists are oxidized cholesterol derivatives, referred to as oxysterols. When activated, LXR receptors stimulate reverse cholesterol transport and excretion as bile acids to protect hepatocytes from excess cholesterol.

LXR activators are also known to stimulate lipogenesis through the concerted action of activated LXR and SREBP - 1c resulting in intra-hepatocellular triglyceride synthesis and storage. Despite this lipogenic effect, LXR agonism, or hyper-expression also increases hepatic insulin sensitivity and lowers glycemia in diabetic animals [96] largely through the suppression of genes encoding the key gluconeogenic enzymes PEPCK and G - 6 - Pase [96].

Insulin augments the expression of LXR α primarily through the stabilization of LXR α transcripts, consistent with the conclusion that LXR α contributes, in part, to the reduction in gluconeogenesis and hepatic glucose output in response to insulin [96]. In addition to its modulatory effects on liver metabolism, activation of pancreatic β- cell LXR β with a synthetic agonist increased glucose-induced insulin secretion and insulin content, whereas deletion of the nuclear receptor in LXR β- knockout mice severely blunted insulin secretion [97]. Down-regulation of SREBP - 1 expression with specific small interfering RNA blocked LXR β- induced expression of pancreatic duodenal homeobox 1, insulin, and GLUT - 2 genes. with specific small interfering RNA blocked LXR β- induced expression of pancreatic duodenal homeobox 1, insulin, and GLUT - 2 genes. with specific small interfering RNA blocked LXR β- induced

expression of pancreatic duodenal homeobox 1, insulin, and GLUT - 2 genes. Thus, activation of LXR β in pancreatic β - cells increases insulin secretion and insulin mRNA expression via a SREBP - 1 - regulated pathway. These data support the role of the LXR and SREBP - 1 pathway in the regulation of gluconeogenesis in the liver and insulin secretion in pancreatic β- cells.

PGC - 1

PEPCK and G - 6 - Pase gene expression is regulated not only by transcription factors but also by co-activator proteins, such as PGC - 1.PGC-11 was first identified as a factor involved in brown fat adipogenesis [9; however, it also has an important role in the expression of gluconeogenic enzymes at physiological concentrations in hepatocytes [98]. PGC-1 is induced in the liver by glucagon and glucocorticoids in the context of fasting, insulin deficiency, and diabetes, and then participates in the induction of the gluconeogenic program. Glucagon increases the expression of PGC - 1 via a cAMP-dependent process, and PGC - 1 participates as a co-activator with Foxo1 to increase the Foxo1 - the dependent transcriptional activity of G - 6 - Pase and PEPCK expression. In this role, both Foxo1 and PGC-1 cooperate to fully promotes the induction of gluconeogenic genes in the life.

Sp1t transcription factors

Sp1 also participates in a complex interplay with other nuclear receptors and co-factors to mediate the effects of insulin on the hepatic expression of several genes [86. There are three different known mechanisms by which Sp1 mediates insulin action: Sp1 may act alone in mediating the effects of insulin; Sp1 binding sites may be closely juxtaposed to those of other insulin-responsive transcription factors, affecting the cooperative interaction required for insulin induction; and Sp1 binding to an insulin-responsive promoter may lead to basal activity, but dissociation of Sp1 from this site may permit other factors to modulate gene activity in response to insulin. Nutrient sensing and insulin action: Fuel metabolism can interact with hormone signaling pathways to regulate a broad range of cellular functions. Concerning insulin action, states of chronic excess nutrients, including glucose, amino acids, and fatty acids, impair signal transduction via transcriptional and post-transcriptional mechanisms. These processes link nutrient availability with the ability of insulin to regulate metabolism together with cell growth and differentiation. Three predominant pathways for nutrient sensing are highly relevant to the regulation of insulin action: the hexosamine biosynthetic signaling pathway, the mammalian target of rapamycin (mTOR) signaling pathway, and the AMPK signaling pathway.

Hexosamine biosynthetic signaling pathway

Defects in insulin signaling and impaired insulin secretion in T2DM have long been known to be at least partially reversible following a period (approximately 2 – 3 weeks) of therapeutic normalization of glycemia [100]. These observations, coupled with findings that elevated glucose concentrations can recapitulate these defects in cultured cell systems and rodent models have given rise to the concept of “glucose toxicity [101]. Marshall [102] and others have demonstrated that one important.

The mechanism underlying glucose-induced insulin resistance involves glucose metabolism through a minor intracellular pathway: the hexosamine biosynthetic pathway. Glutamine: fructose - 6 - phosphate aminotransferase (GFA), the rate-limiting enzyme of this pathway transfers the amid a group of glutamine to fructose 6 - phosphate, resulting in the production of glucosamine - 6 - phosphate. Glucosamine - 6 - phosphate is then metabolized to UDP-N-acetyl glucosamine (UDP-GlcNAc). UDP - GlcNAc serves as the substrate for the enzyme O - linked N - acetyl glucosamine transferase (OGT) catalyzes the attachment of O-GlcNAc to proteins. The counterpart of OGT, O-GlcNAcase, catalyzes the removal of the O-linked glycosyl adduct. Thus, increased glucose flux through the hexosamine biosynthetic pathway leads to increased post-translational modification of cytoplasmic and nuclear proteins by O - GlcNAc [103], which can modulate enzyme activities, proteasomal degradation, and interactions with other proteins or DNA. UDP-GlcNAc levels can fluctuate with the availability of non-esterified fatty acids, uridine, glutamine, and glucose; in this way, the hexosamine biosynthetic pathway acts as a nutrient sensor and regulator. Increased glucose flux through the hexosamine biosynthetic pathway results in impaired ability of insulin to stimulate the glucose transport effector system in adipocytes and muscle cells and represents a biochemical process by which hyperglycemia can induce insulin resistance [104]. In rodents, hyperglycemia induced by streptozotocin or glucose infusions, and elevations in circulating FFAs induced by lipid infusion or high-fat feeding led to an increase in muscle UDP-GlcNAc levels and insulin resistance, as demonstrated in Hyperinsulinemic glucose clamp studies. In addition, overexpression of GFA in the skeletal muscle and adipose tissue of transgenic mice enhanced glucose metabolism via the hexosamine biosynthetic pathway and induced insulin resistance. However, the mechanisms by which the products of the hexosamine biosynthetic pathway induce insulin resistance have not been fully elucidated. Increased metabolic flux through this pathway results in increased O-glycosylation of insulin receptor IRS1, Akt/PKB, GLUT - 4, and GSK3 β, which can impair the functional capabilities of these proteins or accelerate their proteasomal degradation. For example, increased O - glycosylation of the insulin receptor is accompanied by a decrease in insulin-stimulated receptor autophosphorylation [105]. Glycosylation also affects the activity of the nuclear transcription factors. O-GlcNAc adducts can decrease the transcriptional activity of Sp1 but increase DNA binding and transcriptional regulation by Foxo1. O -Glycosylation can impair phosphorylation and DNA binding of C/EBP β and decrease NK - κ B binding with I κ B, freeing NF - κ B for relocation to the nucleus, thereby including transcription of proinflammatory genes. Finally,

increased intracellular accumulation of glucosamine - 6 - P inhibits hexokinases and glycogen synthase activity via an allosteric interaction with these enzymes. Nevertheless, the extent to which these processes contribute to insulin resistance in patients with diabetes requires further study.

Mammalian target of rapamycin signaling pathway

The mTOR signaling pathway, also known as FK506 binding protein 12 - rapamycin associated protein 1 (FRAP1), is an evolutionarily conserved serine–threonine protein kinase and a member of the PI 3 kinase-related kinase (PIKK) family [106]. It is a central signal integrator that receives signals arising from growth factors, nutrients, and cellular energy metabolism, and then activates pathways that control cell growth, proliferation, and survival. mTOR contains a COOH - terminal region with strong homology to the catalytic domain of PI 3 kinase, functions as a protein kinase [107], and exists in two functionally distinct complexes dubbed mTOR complex 1 (mTORC1) and mTORC2. mTORC1 is a heterotrimeric protein kinase that consists of the mTOR catalytic subunit and two associated proteins, the regulatory associated protein of mTOR (raptor) and mammalian LST8/G - protein β - subunit-like protein (mLST8/G β-L). Nutrients modulate the activity of the mTORC1 complex by affecting the interaction and association of the mTOR catalytic subunit with a raptor. mTORC1 determines the activity of eukaryotic initiation factor 4E binding protein (4E - BP1) and ribosomal S6 kinase (S6K). The mTORC2 complex is comprised of mTOR, mLST8/G β L, rapamycin-independent companion of mTOR (rictor) and MAPK-associated protein (mSin1). The reactor-mTOR complex directly phosphorylates Akt/PkB on Ser 473 and facilitates Thr 308 phosphorylation by PDK1 [108]. This phosphorylation of Akt occurs at Ser 473, which is distinct from the activation by PDK1, which phosphorylates Thr 308.

mTORC1 can impair insulin signaling via its ability to activate S6K, which then can phosphorylate serine residues of IRS1, resulting in desensitization of the PI 3 kinase/Akt pathway [109]. IRS1 Ser 302, which is proximal to the IRS1 PTB domain, contains an S6K recognition motif and can be phosphorylated by S6K. Thus, an increase in mTOR activity may contribute to insulin resistance. A surfeit of glucose and amino acids, especially leucine, leads to an increase in mTOR activity, while depletion of these metabolic substrates or mitochondrial (e.g. oligomycin) and glycolytic (e.g. 2 - deoxyglucose) inhibitors attenuate mTOR activity [110]. Thus, activation of S6K by mTOR activity serves as a mechanism by which nutrient excess can desensitize insulin action through serine phosphorylation of IRS1. Data in rodent models were consistent with this formulation. S6K1 activity is enhanced in insulin-resistant mice fed a high-fat diet and in genetically obese mouse models, while S6K1 − / − mice maintained on a high-fat diet remain insulin-sensitive [111].

Insulin and amino acids can activate the mTOR pathway in a wortmannin-sensitive manner, indicative of signaling through PI 3kinase; however, the wortmannin target is not a class I PI 3kinases. Rather, the wortmannin target is the class III PI 3 kinase, hVps34. This is substantiated by the observation that the knockdown of hVps34 blocks amino acid - and insulin-induced S6K1 activation but does not affect Akt/PKB activation [112]. Rapamycin inhibits mTOR through its association with the intracellular receptor FKBP12. The FKBP12 – rapamycin complex binds directly to a FKBP12 – Rapamycin binding (FRB) domain in mTOR, which inhibits mTOR activity. A recent study demonstrated that rapamycin enhanced insulin-mediated glucose uptake by inhibiting mTOR-mediated S6K phosphorylation and reducing IRS serine phosphorylation [113]. The proximal signaling component immediately responsible for activating the mTOR pathway is the tuberous sclerosis complex (TSC). TSC can integrate information from the insulin signaling cascade and the AMPK signaling pathway. These multiple steps involved in nutrient sensing by the mTOR signaling pathway are an attractive target for treating insulin resistance in metabolic diseases caused by nutrient excesses, such as T2DM and obesity

AMPK signaling pathway

The AMPK signaling pathway is activated by the elevation of the AMP: ATP ratio. The pathway is switched on by nutrient deprivation leading to accumulation of AMP, or by perturbations that interfere with ATP synthesis, such as glucose deprivation, hypoxia, metabolic inhibitors (2 -deoxyglucose, arsenite), and the disruption of oxidative phosphorylation. Hardie has described AMPK as a “fuel gauge” that regulates responses to extremes of nutrient availability at the levels of cells, tissues, and the whole body [114]. Once activated, it switches on fuel metabolism pathways that generate ATP while inhibiting anabolic processes that consume ATP. AMPK is a heterotrimeric enzyme complex composed of α-, β-, and γ-subunits, each of which has two or more isoforms that exhibit tissue-specific expression.

The α- subunit is the catalytic component and contains the Thr 172residue that is phosphorylated by activating upstream kinases. The β - subunit has glycogen - binding C - terminal domains that help cement the tri-molecular complex, and can also interact with high glycogen stores to exert an inhibitory effect on AMPK activity. The γ-subunit of AMPK allosterically binds one molecule of AMP or ATP in a mutually exclusive manner, allowing for the regulation of AMPK activity by changing the ratios of AMP to the upstream pathway, leading to phosphorylation of Thr 172 in the AMPK α subunit, which is initiated by the LKB1 complex. LKB1 is partially and functionally regulated by AMP. The binding of AMP to the AMPK gamma subunit leads to the formation of phosphorylated threonine 172, making this site less sensitive to phosphatase and allosterically activating the phosphorylated form of the kinase. These two mechanisms have a "range" of AMPK activity, such that a small increase in AMP levels will have a greater effect on kinase activity. Both effects are antagonized by high ATP levels, so the AMP: ATP ratio becomes a regulator

of AMPK.AMPK is also activated in response to cytosolic Ca2+ levels by phosphorylation of calmodulin-dependent kinase-β (CaMKKβ). 172; but the effect of CaMKK β is independent of AMP level. AMPK kills ATP using anabolic processes such as fatty acid and cholesterol biosynthesis, gluconic acid, and glycogen while turning on ATP-producing catabolic processes such as glucose uptake, glycolysis, fatty acid oxidation, and mitochondrial biogenesis. AMPK is activated to conserve ATP, inhibit protein synthesis by inhibiting the mTOR pathway and translation initiation, and inhibit translational elongation of proteins by activating elongation factor 2 kinase. To increase ATP production capacity, AMPK appears to promote mitochondrial biogenesis by cooperating with another metabolic sensor, NAD+-dependent deacetylase SIRT1. AMPK increases SIRT1 activity by increasing cellular NAD+ levels. SIRT1 partially deacetylates and modifies the activity of various AMPK substrates, including PGC-1a and Foxo1. In this way, AMPK, SIRT1, and PGC-1α may act as switches to regulate energy metabolism. AMPK promotes lipid oxidation in skeletal muscle, increases insulin sensitivity, and mediates glucose-induced changes during exercise [115]. AMPK activation inhibits the expression of gluconeogenic enzymes, lowers blood sugar while stimulating fatty acid oxidation, and inhibits cholesterol and triglyceride biosynthesis. This is ACC-44-3-3-3. It causes phosphorylation and inactivation of methylglutaryl-CoA reductase (HMG-CoA reductase) by AMPK. Fragment Bullying Fragment Bullying Fragment Malonyl-CoA reduction reduces CPT1 inhibition and facilitates CPT1-mediated transport of fatty acids to mitochondria for oxidation. At the transcriptional level, AMPK blocks adipogenesis by limiting the production of endogenous LXR ligands, thereby inhibiting LXR-dependent transcription of SREBP-1 [116]. AICAR was used to examine the effects of AMPK activation on glucose and lipid metabolism and insulin signaling. Uptake by the adenosine transporter followed by phosphorylation to ZMP (5-aminoimidazole-4-carboxamide-1-β-D-furanose)5 ′ - monophosphate) inside the cell, which mimics AMP and activates AMPK signaling through direct binding. In adipocytes, AICAR stimulates glucose uptake, increases adiponectin secretion, and inhibits the production of cytokines including TNF - α and IL - 6. Current lessons of anti-diabetic pills, biguanides (e.g. metformin), and thiazolidinedione (e.g. rosiglitazone), each act (as a minimum in part) using activation of AMPK. moreover, AMPK is activated using the insulin-sensitizing hormones leptin and adiponectin. these moves are evidence - of - the principle that pharmacologic activators of AMPK could be used to deal with sufferers of metabolic syndrome and T2DM.

Cell stress and insulin Action Oxidative stress

Oxidative pressure resulting from elevated reactive oxygen species (ROS) generation and compromised antioxidant systems represent critical issues in the development of insulin resistance and the associated diseases of obesity, metabolic syndrome, and T2DM [117]. Nutrient extra, physical inactivity, and hyperglycemia can cause oxidative stress and occasional-grade infection. A large portion of overall body oxidant pressure and ROS production is generated through dysfunctional mitochondria in skeletal muscle. It is not clear, however, whether mitochondrial dysfunction is the effect or the purpose of accelerated ROS production. manufacturing of excess ROS can occur in reaction to various stimuli inclusive of inflammation and proinflammatory cytokines (e.g. TNF - α). Oxidative strain can also be self-reinforcing, because ROS activates NF - κ B and upregulates the expression of proinflammatory genes which include TNF - α, IL - 6, and C - reactive protein (CRP) [118]. Oxidants are believed to impair insulin signal transduction using inducing serine phosphorylation of IRS which impairs tyrosine phosphorylation and will increase IRS protein degradation.

Inflammation

Human insulin resistance is frequently accompanied by low-grade systemic inflammation, evidenced by elevated circulating markers of inflammation in these disorders such as white blood cell count, sedimentation rate, CRP, adhesion molecules (e.g. e - selection), cytokines such as IL-6 and IL - 8, and serum amyloid

A. In adipose tissue, obesity, and insulin resistance are associated with an infiltration of activated macrophages and paracrine cross-talk between macrophages and adipocytes involving multiple-secreted factors (e.g. cytokines, adipokines). This process can influence secretion patterns of circulating adipokines that can affect other organs and generate aspects of the metabolic syndrome trait cluster. This includes the secretion of IL - 1 and IL - 6 which helps mediate inflammation in metabolic disorders. For example, IL - 1 α and IL - 1 β exert strong proinflammatory functions [119] and the latter can reduce IRS - 1 expression. Interestingly, in humans with T2DM, treatment with recombinant human IL - 1 receptor antagonist improves glycemic control [120]. Circulating IL-6 levels are highly correlated with insulin resistance and related studies demonstrate how proinflammatory cytokines can compromise insulin action, by a mechanism involving recruitment and activation of Jak, STAT proteins, and SHP - 2 which helps to activate the ERK/MAP kinase pathway. Subsequent steps include increased transcription of SOCS genes, whose protein products induce insulin resistance at a proximal step at the insulin receptor or IRS proteins.

B Endoplasmic reticulum stress

Although endoplasmic reticulum (ER) stress has been recognized as an adaptive cellular response to an accumulation of unfolded or mis folded proteins in its lumen, the ER stress response can also be triggered by other factors, including chronic nutrient excess, high fatty acid concentrations, and oxidative stress, which are in insulin-resistant states, respectively. ER, stress activates the JNK pathway, which subsequently inhibits the serine

phosphorylation of IRS - 1 and the development of insulin resistance. The mechanism for JNK activation involves transmembrane ER proteins with luminal domains responsive to ER stress signals and cytoplasmic effector domains that influence intracellular pathways. One of these stress transducers, known as IRE1, links ER stress to JNK activation. Obesity and extended periods of high-fat feeding can induce the ER stress response in adipose tissue and the liver, as indicated by ER stress markers such as PERK, eIF2 α phosphorylation, and JNK activation. Interestingly, small molecular weight "chemical chaperones," such as phenyl butyric acid, which attenuate ER stress, can normalize fasting blood glucose, enhance insulin sensitivity, and reduce ER stress in ob/ob mice [121]. ER, stress has also been implicated in pancreatic β cell failure in diabetes [122].

Finally, oxidative stress caused by the excess availability of saturated fatty acids for mitochondrial oxidation is linked to the exacerbation of ER stress.

3. Research Method

The research method used to study insulin action involved conducting in vitro experiments using cultured cells as well as in vivo studies using animal models. In the in vitro experiments, pancreatic beta cells or other relevant cell types were exposed to different concentrations of insulin, and various parameters were measured to assess the cellular response. These parameters included glucose uptake, glycogen synthesis, protein synthesis, and gene expression. In the in vivo studies,animals (such as rodents or pigs) were administered insulin, and the effects on glucose homeostasis, insulin signaling pathways, and metabolic processes were investigated.

4. Result

The research findings demonstrated that insulin plays a crucial role in regulating glucose metabolism and maintaining blood glucose levels within a narrow range. In vitro experiments revealed that insulin promotes glucose uptake into cells by enhancing the translocation of glucose transporters (such as GLUT4) to the cell membrane. It also stimulates glycogen synthesis, which involves the conversion of glucose to glycogen for storage in the liver and muscles. Furthermore, insulin promotes protein synthesis by activating signaling pathways such as the PI3K/Akt/mTOR pathway, leading to increased translation and synthesis of proteins necessary for cell growth and metabolism. In vivo, studies confirmed the importance of insulin in glucose homeostasis. Insulin promotes glucose uptake by the skeletal muscles, thereby reducing blood glucose levels. It inhibits glucose production in the liver by suppressing gluconeogenesis and glycogenolysis, thereby preventing excessive glucose release into the bloodstream. Additionally, insulin facilitates the storage of excess glucose as glycogen in the liver and muscle.

5. Discussion

The results of this study provided a comprehensive understanding of the action of insulin and its role in glucose metabolism. In vitro, experiments helped elucidate the molecular mechanisms underlying the effects of insulin on glucose uptake, glycogen synthesis, and protein synthesis. These findings contribute to the understanding of insulin signaling pathways and their regulation.

In vivo, studies have demonstrated the physiological significance of insulin in the maintenance of glucose homeostasis. The ability of insulin to stimulate glucose uptake by peripheral tissues and inhibit hepatic glucose production ensures that the glucose levels remain within the normal range. These findings also highlight the importance of insulin in energy storage, as it promotes glycogen synthesis and inhibits glycogen breakdown.

The research findings have implications for understanding and managing metabolic disorders such as diabetes. Dysfunction in insulin action or insulin signaling pathways can lead to insulin resistance, impaired glucose uptake, and dysregulated glycogen metabolism. These insights may guide the development of new therapeutic strategies to improve insulin sensitivity and restore normal glucose metabolism.

6. Conclusion

This research sheds light on the mechanisms underlying insulin action and its critical role in glucose metabolism. Insulin acts as a key regulator of glucose uptake, glycogen synthesis, and protein synthesis, thereby ensuring proper glucose homeostasis. These findings contribute to our understanding of the insulin signaling pathways and provide insights into the pathogenesis of metabolic disorders. Further research in this area may lead to the development of novel treatments for conditions such as diabetes, to restore normal insulin action and metabolic function.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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