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EC PHARMACOLOGY AND TOXICOLOGY
Review Article

Insulin Resistance: Recent Advances in Pathogenesis, Molecular Mechanisms and Clinical Relevance

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Received: August 18, 2017; **Published:** October 20, 2017

Abstract

Insulin resistance is a complex metabolic disorder. There are various factors involved in aetiology, pathogenesis and pathophysiology of insulin resistance. Therefore, the present review has been written to provide critical information about insulin resistance corresponding for better understanding of pathogenesis and pathophysiology hallmarks, markers as well as exploitation of better drug targets. However, there are some recent reports suggesting the role of microRNA, histone deacetylase, and toll like receptors, microbiota and short chain fatty acids in the pathogenesis of insulin resistance. The role of insulin resistance has been established in brain which is termed as type 3 diabetes (in Alzheimer's disease patients). The review provides a brief understanding on this. A brief description about various markers of insulin resistance is also under the scope of review.

Keywords: *Insulin Receptor (IR); Insulin Receptor Substrate (IRS); Insulin Resistance; Insulin Signalling; Oxidative Stress; Pathogenesis; Pathophysiology*

Introduction

Insulin resistance, a complex metabolic disorder, in which there is no response to insulin in circulation by pancreatic cells. Although, production of insulin in the body remains normal, but the cells lack its ability to use it as they become resistant, that result in rise in blood sugar level. There is a subsequent increase in insulin production by beta cells in the pancreas, resulting in rise of blood insulin level. This leads to type 2 diabetes, as it remains unnoticed [1].

Diabetes mellitus (DM) is depicted by a hyperglycemia as a consequence of deficiency in insulin secretion or resistance or both [2]. Type 2 diabetes mellitus (T2DM) was earlier more prevalent in older age people. But nowadays, T2DM is prevalent at any age. Thus need for its treatment is becoming urgent as the diabetic population is increasing worldwide at an alarming rate [3].

In non-diabetic individuals, the insulin resistance has been found to involve various other health problem/complication such as dyslipidaemia and obesity. Although, there are various investigations presently going-on on insulin resistance, but the precise mechanism has not been comprehended yet. Therefore, in the present article, the authors have made significant efforts to highlight the aetiology, complex pathogenesis and pathophysiology of insulin resistance along with various biomarkers.

As per a national survey, insulin resistance syndrome have affected about 24% of US people with age greater than 20 years [4]. The prevalence of diabetes mellitus is increasing, expected to reach up to 165% or more by 2050 in United States alone. Globally, an estimate of 2013 suggested that around 382 million individuals will endure diabetes with prevalence of 8.3%. In 2014, the prevalence of diabetes was estimated to be 9% among adults globally. Among whole population almost 9% of adults suffer from diabetes that was assessed in a

survey done on 2014. The prevalence of T2D is around 371 million worldwide, which is expected to increase up to 550 million by 2030 as per the data estimated by International Diabetes Foundation (http://www.idf.org/diabetesatlas/5e/Update 2012).

Aetiology

The causes resulting in raised frequency of insulin resistance can be broadly categorised based on genetic factors as well as environmental factors.

Genetic Factors

Insulin has pleiotropic effects. Pleiotropic is when a single gene influences multiple traits. The genes directing insulin sensitivity are genetically in correspondence to HDL cholesterol, triglycerides and body mass index (BMI) [5]. Gene encoding proteins involved in the complex signal transduction of insulin, might be responsible for insulin resistance. Evidence has shown that defect in these genes brings about decreased insulin action and lowered uptake of glucose [5]. Insulin resistance is caused by knockout genes that can be further subdivided as (Table 1-3).

S. No.	Gene	Phenotypes
1.	**Gene Encoding proteins**	
	IR knock out animals	
	Heterozygous ($IR^{+/-}$)	No change in Glucose, Insulin conc. and glucose tolerance
	Homozygous ($IR^{-/-}$)	Diabetes and died in 3-7 days
	IRS-1 knock out animals	Insulin resistance
	IRS-2 knock out animals	Insulin resistance and β-cell dysfunction
	IRS-3 & IRS-4 knock out animals	No significant effect
2.	**Tissue Specific**	
	MIRKO mice	Decreased Insulin receptor expression
	LIRKO mice	Severe Insulin resistance, constant glucose production
	FIRKO mice	Protective action for Obesity and Insulin resistance

Table 1: *Insulin resistance caused by genetic mutation and knockout models.*

Sr. No.	Test	Value in IR	Normal range
1.	Fasting blood sugar and Postprandial blood sugar	More than normal values	< 100 mg/dl (fasting) < 140 mg/dl (postprandial)
2.	Fasting insulin assessment	> 25 ml IU/L or > 174 pmol/L	
3.	Glucose tolerance testing		
	Parameter- Postprandial glucose	7.8 - 11.0 mMol/L or 140 - 197 mg/dl (impaired glucose tolerance) 11.1 mMol/L or 200 mg/dl (diabetic)	< 7.8 mMol/L or < 140 mg/dl (postprandial)

Table 2: *Indirect measure of Insulin sensitivity- range (normal as well as in insulin resistance).*

S. No.	Method	Comments	Advantages	Disadvantages
1	Hyperinsulinemic euglycemic glucose clamp	Gold standards for quantifying IR	Direct measure	Laborious, frequent blood sampling
2	OGTT	Clinically used method	Help in estimating other index	Useful for glucose tolerance but not for IR
3	Fating insulin	Most practical method	Detects IR before clinical disease appears	Lack of insulin assay procedure
4	HOMA	Assesses inherent β-cell function and insulin sensitivity	Simple, minimally invasive, predicts fasting steady state-Glucose levels	Needs further validation
5	QUICKI	Mathematical transformation of FBG and insulin	Consistent, precise index of insulin sensitivity, minimally invasive	Normal range to be established for each laboratory due to significant inter laboratory variations

Table 3: *Advantages and Disadvantages of Measures of insulin resistance.*

IR caused by knockout genes a) Genes encoding proteins and b) Tissue specific

Genes encoding proteins

IR knock out animals

The binding of insulin to the insulin receptor (IR) encoded by the INSR gene (Insulin receptor gene) produces action. In case of IR knock out animals, i.e. heterozygous mice (IR+/-), the concentration of glucose and insulin in glucose tolerance remain same as compared to wild-type mice [6]. However, in case of homozygous mice, a rapid development of diabetes (IR-/-) have been seen and they died within 3-7 days [6].

IRS-1 knock out animals

IRS-1, insulin receptor substrate, plays a principal role for producing insulin response. Impairment in glucose metabolism from β-cells has been seen in IRS-1 gene knockout animals. However, this impairment is limited to some extent because of additional substrate IRS-2 that runs the insulin signalling pathway [7].

IRS-2 Knockout animals

IRS-2 disrupted allele mice developed diabetes due to the combined effect of insulin resistance and disrupted pancreatic β-cell function [8]. Thus various other substrates are required to drive insulin signalling pathway (see Figure 1), as the phenotype due to the absence of IR-gene knockout is more extreme than IRS-2 gene knockout.

IRS-3 and IRS-4 gene knockout

The outcome of the work of IRS-1 and IRS-2 gene knockout encouraged to analyse the phenotype of IRS-3 and IRS-4 gene knockout. The studies has demonstrated their insignificant role as no alteration have been seen in glucose tolerance, glucose and insulin concentrations [9,10].

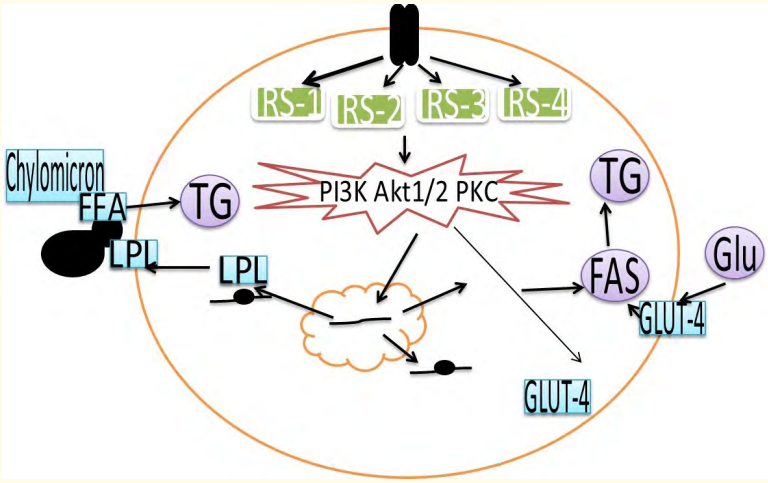

Figure 1: *Insulin receptor substrate-1-4- signalling pathway. FAS-Fatty acid synthase complex; FFA-Free Fatty Acids; GLUT-4-Glucose transporter type 4; Glu-Glucose; IRS-Insulin receptor substrate; LPL-Lipoprotein lipase; PI3K-Phosphatidylinositol 3-kinase; TG-Triglyceride.*

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Tissue specific IR in knockout animals

MIRKO mice

Muscle specific Insulin receptor knockout mice, i.e. GLUT-4 deficient and IR-deficient. These mice showed decreased insulin receptor expression in 95% skeletal muscle. The levels of triglyceride and free fatty acids have shown significant increase, but no change has been observed in the level of glucose, insulin and glucose tolerance [11].

LIRKO mice

Liver specific insulin receptor knockout mice causes rapid Insulin resistance and constant glucose production via gluconeogenesis and glycogenolysis [12].

FIRKO mice

Fat insulin receptor affects mass of adipose tissue that has been seen to decrease in fat insulin receptor knockout mice thus seemed to protect against obesity and insulin resistance. Also, the life span was increased by 18% [13].

Environmental factors

Diet

The presence of obesity in diabetic patients is very common. The presence of saturated fatty acids (SFA) in diet effect insulin resistance badly as compared to monounsaturated fatty acids (MUFA) (Steven., *et al*. 2006). Raised levels of triglycerides and free fatty acids in tissues and blood stream have been found to reduce insulin sensitivity.

The basis of obesity and insulin resistance remains the same that is systematic surfeit, due to a repeated excess of glucose, fructose levels and fats. Elevated glucose levels stimulates insulin secretion; and triglyceride levels are raised in the bloodstream by fructose; and fats get absorbed easily by the adipose cells, ending up as fatty tissue in a hyper caloric diet. However, presence (in surplus of 5 - 10% of total fat intake) of polyunsaturated omega-3 fatty acids in diet abolishes the effect of high-fat diet [14].

Sedentary lifestyle

Sedentary habit increases the possibility of becoming insulin resistant [15]. Lifestyle intervention like taking low-calorie and indulging in physical activity decreases the possibility of type 2 diabetes. A study demonstrated that exercise done for at least a week vigorously decreases the possibility of type 2 diabetes in women up to 33%. Also, a study has shown that cigarette-smoking aggravate insulin resistance in patients of type-2 diabetic [16].

Stress (oxidative stress)

Impaired insulin signalling causes insulin resistance. Reactive oxygen species (ROS) results in altered insulin signalling by causing phosphorylation at serine/threonine site of the IRS. The cellular reorganization of insulin signalling and mitochondrial activity is disturbed and GLUT4 gene transcription is decreased, resulting in insulin resistance [17,18].

Insulin Signalling

Insulin receptor belongs to a tyrosine kinase family. Insulin receptor have a heterotetrameric glycoprotein structure containing four subunits α, β (two each) that are linked together by disulphide bonds. Insulin binds to its receptor and undergoes autophosphorylation along with β subunits which is located intracellularly [18]. This in-turn activates insulin receptor which causes phosphorylation of insulin receptor substrates at tyrosine site (IRS-1-4) [19] that further serve as binding sites for signalling molecules which have SH-2 (Src-homology-2) domains. The complex so formed brings about downstream signalling. PI3K binds to IRS proteins because of the presence of p85 regulatory and p110 catalytic subunit. In consequence of this, substrate gets phosphorylated that is PtdIns (4,5) P2, on inositol ring 3'position to generate PtdIns (3,4,5) P3. These further recruit the serine kinases to the plasma membrane. The concerned serine kinases are PDK-1, PKB/Akt, and PKC. These serine kinases induces various responses as by insulin i.e. GLUT4 translocation to the plasma membrane, lipogenesis by activation of fatty acid synthase gene and glycogen synthesis by phosphorylation of GSK-3. In addition, mitogen activated protein kinase and ERK are activated [18].

Pathogenesis of insulin resistance

Glucose absorption occurs by GLUT4 in adipose tissue, skeletal muscle and liver. In the liver, insulin governs glycogen synthesis and as soon as the glucose level reaches to maximal, glucose moves to adipose tissues in the form of lipoproteins. In adipose tissue, fatty acid synthesis occurs but gluconeogenesis remain halted. Insulin inhibits lipase thus cause inhibition of fatty acids [20].

In fasted state, glucose level decreases in correspondence to which insulin level also decreases that in turn increases hepatic gluconeogenesis (glucose from non-carbohydrate sources), promotes glycogenolysis (glycogen to glucose-1-phosphate, glycogen) but lipid production in liver diminishes while in adipose tissue lipolysis increases [21].

Several mechanisms have suggested the pathogenesis of insulin resistance which includes ectopic lipid accumulation, inflammatory pathways, sleep deprivation, oxidative stress and AGE products.

Ectopic lipid accumulation

Triglycerides storage in non-adipose tissue is called ectopic lipid storage, which usually is in small amount. Ectopic lipid accumulation mainly occurs in skeletal muscle, liver and heart. The accumulation of triglycerides in the muscle indicates resistance of insulin in muscle. Accumulation of lipid in muscle i.e. diacylglycerols activates novel PKC (nPKC) isoform PKC θ, PKC Ɛ [22] which directly causes impairment of insulin signalling and promotes insulin resistance [23]. Fatty acid inhibits pyruvate dehydrogenase enzyme that reduces glucose oxidation and causes accumulation of glycolytic intermediates impairing uptake of glucose in muscle through insulin [24]. Triglycerides storage in non-adipose tissue is called ectopic lipid storage, which usually is in small amount. Ectopic lipid accumulation mainly occurs in skeletal muscle, liver and heart. The accumulation of triglycerides in the muscle indicates resistance of insulin in muscle. Accumulation of lipid in muscle i.e. diacylglycerols activates novel PKC (nPKC) isoform PKC θ, PKC Ɛ [22] which directly causes impairment of insulin signalling and promotes insulin resistance [23]. Fatty acid inhibits pyruvate dehydrogenase enzyme that reduces glucose oxidation and causes accumulation of glycolytic intermediates impairing uptake of glucose in muscle through insulin [24].

Also, when DAG levels are raised in liver cells, PKC activation occurs, it leads to decrease in insulin receptor kinase activity and decreased insulin-stimulated IRS2 tyrosine phosphorylation and IRS2-associated PI3K activity. These changes leads to insulin resistance through various cellular mechanism [25].

In heart, the raised FFA supply results in decreased oxidation. This decreased oxidation, results in lipid intermediates which impairs insulin signalling, hence, GLUT-4 involved glucose uptake [26].

Inflammation and insulin resistance

In insulin signalling, the activation of jun-N-terminal kinase 1 (JNK1) brings about pathological changes by phosphorylation of IRS1 at serine residue at 307 site. This results in disturbance in normal insulin signalling pathway providing a possible relation between insulin resistance and inflammation [27].

Obesity and high fat diet activate IKKβ/NF-kB and JNK pathways in adipocytes, hepatocytes and associated macrophages. Various ligand activate inflammatory pathway including ligands for IL-1, TNF-α, Toll, or AGE receptors, IL-1R, TNFR, TLR, or RAGE, respectively [28].

Also, activation of IKKβ causes NF-κB translocation, which promotes increased transcription of activator proteins (AP-1) and causes increased expression of potent inflammatory mediators that can cause insulin resistance [29]. Insulin signalling is disrupted, causing resistance of insulin in the cell [30].

Oxidative stress and insulin resistance

Oxidative stress plays a pivotal role in insulin resistance [30]. Various mechanism like sleep deprivation and inflammatory cascade involves oxidative stress, which leads to insulin resistance [31]. Lipid accumulation in adipocytes causes Angiotensin-II to activate NADPH oxidase. This mechanism leads to increase in production of various inflammatory mediators like TNF-α, IL-6. These inflammatory mediators further leads to various pathways resulting in insulin resistance [32].

Similarly, ROS causes defective insulin signalling via phosphorylation at serine/threonine sites of IRS that results in firstly, cellular reorganization of insulin signalling components is disturbed; second, transcription of GLUT4 gene has been reduced, and mitochondrial activity has been altered [18]. GLUT4 gene, a glucose transporter, expression is decreased that in turn decreases glucose uptake thereby causing insulin resistance [33].

Also, oxidative stress induces several stress-related pathways, like NF-κB, JNK/SAPK and p38MAPK. The NF-kB pathway is activated by serine kinase (IKK) through phosphorylation of IkB i.e. inhibitory subunit. Serine kinase exerts a negative impact on insulin signalling [18].

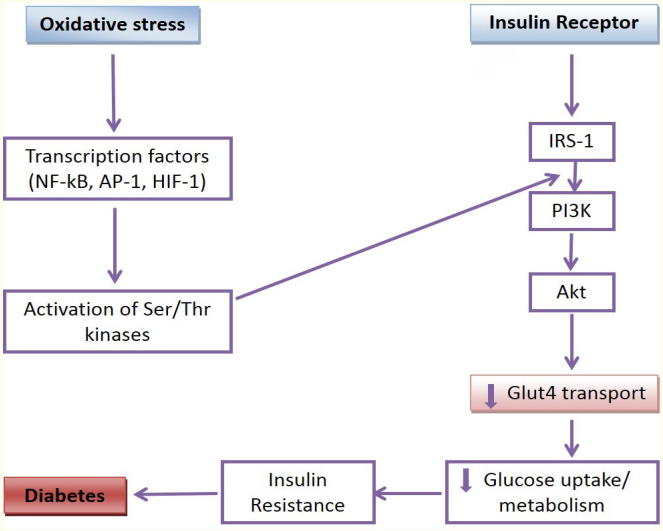

Figure 2: *Oxidative Stress and insulin resistance.*

Sleep deprivation and insulin resistance

Sleep loss is one of the possible cause of being obese and diabetic. The link between sleep deprivation and insulin resistance has been established based on the facts which include impaired metabolism of glucose and increased possibility of diabetes without involvement of body mass index (BMI). Sleep destitution/deprivation produces imbalance in energy which increases weight because of raised appetite (more time to eat). This falls out in insulin resistance, a state that increases risk of diabetes [34].

Sleep loss causes oxidative stress resulting in mitochondria. Mitochondria consumes about 98% of inhaled oxygen [35], from which 0.2 to 2.0% constitute ROS production [36], one of the primal roots of mitochondrial destruction. The disruption of mitochondria causes increased fatty acid oxidation that produces higher levels of fatty acyl-CoA and DAG. Fatty acyl-CoA and DAG consecutively trigger Ser/Thr kinase activity which ultimately produces glucose transport hindrance [37]. Finally, bring about insulin resistance and the risk of diabetes (Figure 3 and 4).

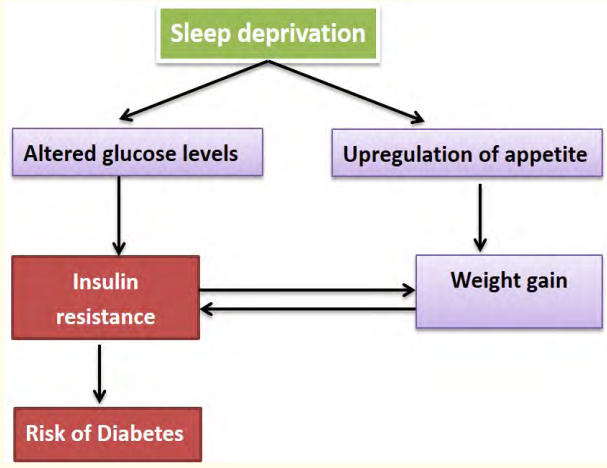

Figure 3: *Molecular mechanisms of sleep deprivation.*

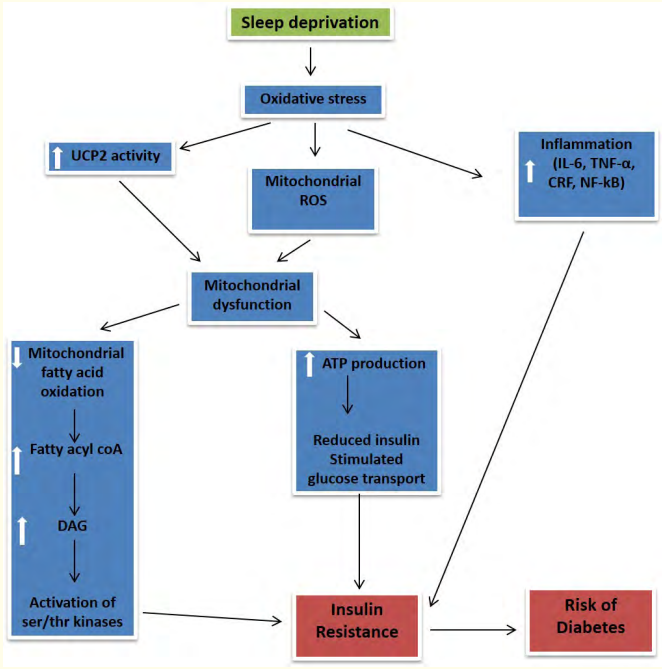

Figure 4: *Molecular Mechanisms of insulin resistance and sleep deprivation.*

Sleep deprivation has been demonstrated to be a prospect for glucose intolerance, obesity, insulin resistance, and T2DM itself [38].

Advanced glycated end product

Higher level of glucose causes glycation of proteins and lipids thereby producing AGEs [39]. AGEs binds to its receptor RAGE that carries out the generation of ROS intracellularly [40] which successively activate NF-kB.

The effect of NF-kB activation combines with the expression of cytokines, along with tumor necrosis factors (TNF-αand TNF-β), interferon-γ and interleukins (IL) 6, 8 and 18, which causes synergism in the advancement of insulin resistance [39].

Recent advances in pathogenesis

MicroRNA – (miRNA)

MicroRNA is short non-encoding RNA that regulates cellular transcriptome and proteome. Several critical biological processes are controlled by miRNA including metabolism, proliferation of cell, programmed cell death i.e. apoptosis and development and progression of disease including inflammation and insulin resistance [41]. Studies have evidenced the involvement of miRNA in development of pancreatic cells such as beta cells [42]. Beta cells containing glucose regulate functional release of insulin, insulin translation and insulin processing through the transcription and stability of insulin mRNA [43]. Also, there is alteration in miRNA transcripts. Foley and O'Neill, proposed the possible role of miR-107 in type 2 diabetes mellitus by its impact on the inflammatory process [44]. Activated macrophages shows down regulation of miR-107 by TLR4 receptors and also, miR-107 has been down regulated in murine and rodent models of obesity and insulin resistance. Thus, decreased miR-107 is an attempt to raise sensitivity of insulin in the resolution phase of inflammation [45].

Histone deacetylase (HDAC)

HDAC is a family of enzymes that along with histone acetyl transferases (HATs) take control over protein acetylation [46]. Inhibition of HDAC activity increases the acetylation of histone and non-histone proteins including NF-kB, MyoD, p53 and N-FAT, that effect gene

expression and protein activity [47]. This results in alteration of different features of cell biology including motility, proliferation, differentiation and apoptosis of cell. HDAC possesses anti-inflammatory activity that can act as drug target for treating insulin resistance [48].

Toll like receptors (TLRs)

TLRs is transmembrane receptors which detects microbial infection and in turn induces various inflammatory and immune response against sustained microbial structures named as pathogen-associated molecular patterns [49]. Among TLRs, TLR2 and TLR4 play an important role in the pathogenesis of insulin resistance and diabetes. TLR-2 andTLR-4 activation cause production of cytokines. TLR4 acts as a molecular link between free fatty acids, inflammation and innate immune response [50].

Microbiota

The mammalian intestine contain a great number of bacteria (approximately 10^{14} bacteria) and as per estimate, the gut microbiota has 100-fold more genes as compared to human genome. These bacteria lives in symbiotic way that also promote disease, in some cases. The lipopolysaccharides (LPS), consist of a lipid and polysaccharide part, acts through toll like receptor 4 (TLR4) is potent activator of pathogen-associated molecular pattern (PAMP) responses [51]. The circulating LPS levels are elevated in the obese mice, which is in direct relation to increased intestinal permeability and reducing activity of zonula occludens-1 (ZO-1), a tight junction protein. This disturbance in junction function leads to leakage of bacterial translocation, resulting in insulin resistance and inflammation [52].

LPS possess both specificity and greater ligand binding affinity for toll like receptors specifically TLR4. Binding of LPS to its receptor activates diverse number of proteins that produces inflammatory effect. LPS from gram negative bacteria specifically bind with TLR4 receptor which reaches sensitive tissue of insulin via gut circulation and mediates inflammatory response thereby protecting host from infection caused by such bacteria. TLR4 has a direct role in insulin resistance further influenced by obesity [53]. LPS reacts mostly with free-fatty acids (FFA) of saturated type. In obese individuals, saturated FFA levels are increased in the circulation due to an increase in lipolysis via adipose tissue, de novo liver lipogenesis and ectopic lipid accumulation. TLRs are linked with gut's microbiota, though single TLR-deficient mice, such as TLR2−/− and TLR5−/− mice, shows gut dysbiosis as compared to the control [54,55]. Various symptoms of metabolic syndrome like elevated blood glucose level, increased insulin resistance and body weight have been related with immune system occurring due to modulation of intestinal flora [56].

The gut microbiota get altered as per excess of nutrition and obesity due to derangement of metabolic system that causes various metabolic disease-associated processes which ultimately produces bacterial products and translocation of which to the circulation increases because of decreased tight junction expression [57]. Besides triggering an immune response, through inflammation and immune cell infiltration of liver and adipose tissue, various other body's tissue are effected by diverse mechanisms that includes deregulation of food intake in the hypothalamus supported by the insulin and leptin resistance and decrease in the anorectic hormones' expression secreted by gut, such as PYY and GLP-1 [58]. Additionally, there is a reduction in the intestinal Fiaf expression influenced by bacteria that alters fat storage and lipid metabolism favouring the obese phenotype [52].

Activation of inflammatory pathways by LPS from gut, mainly via TLR4, increases the inducible nitric oxide synthase (iNOS) expression [59]. In obesity, increased iNOS expression is also observed in insulin sensitive tissues enabling S-nitrosation/S-nitrosylation in which nitric oxide (NO) reacts with cysteine residues thereby forming S-nitrosothiol adducts, thus changing protein function. Thus, LPS induce S nitrosation/S-nitrosylation of the insulin signalling pathway (IR, IRS-1, and Akt), causing insulin resistance in the liver, muscle, and adipose tissue rather than by phosphorylation of IRS-1 at serine residues [60]. The targeted disruption of S nitrosation/S-nitrosylation linked adduct formation prevents insulin resistance and inflammation and consequently improves insulin sensitivity.

Short chain fatty acids (derived from gut microbiota)

Gut bacteria also interact with host system that includes mainly short chain fatty acids (SCFA). SCFA are taken up by host cells through passive diffusion by utilising mono-carboxylic acid transporters, such as monocarboxylate transporters 1 (MCT1) [61]. SCFA acts as anti-

inflammatory molecule such as acetate, propionate and butyrate are capable of inhibiting NF-kB activation in host immune cells by binding to G-protein coupled receptor 43 and 41 (GPR-43 and GPR41), thereby blocking inflammatory response and suppressing TNF-α and IL-6 release, butyrate also reduces IL-12 and increases IL-10 expression [62].

Pathophysiology of insulin resistance

Cellular mechanism

Modification of insulin receptor

The receptor tyrosine kinase family mainly include type-I (IGF-1) receptor (IGF-1R), insulin receptor-related receptor (IRR) and insulin receptor [63]. Insulin receptor i.e. heterotetrameric glycoprotein containing four subunits α, β-subunits (two each) with an extracellular insulin binding site on α subunit. There are extracellular, transmembrane and intracellular domains on β-subunits possessing intrinsic tyrosine kinase activity. The two isoforms of Insulin receptor includes- Isoform A (Ex II+) and Isoform B (Ex II-). The affinity for insulin is two folds higher for Isoform B in comparison to Isoform A. These two isoforms are functionally specific as decrease in its abundance in target tissues may add on to Insulin Resistance [64]. This modification in insulin receptor results in signal transduction defect in insulin action. Due to impaired signal transduction, insulin resistance gets precipitated.

Regulation of glucose transport

Insulin by stimulating GLUT4 (Glucose Transporter 4), results in the release of intracellular glucose to the plasma membrane. The whole process of glucose release involves budding of GLUT4 from the insulin reservoir to the plasma membrane, resulting in docking and fusion with the plasma membrane [65]. Defect in GLUT-4, results in impaired insulin signalling and insulin resistance (Garvey., *et al.* 1998).

Molecular mechanisms

Deregulated secretion of FFA and adipokine

Free fatty acids (FFA) have keen role for causing IR. IR is in correspondence to interleukin 1 (IL-6), elevated tumor necrosis factor α (TNF- α), monocyte chemo attractant protein-1 (MCP-1) and macrophages, adipsin and decreased adiponectin [66].

Adiponectin

Adipose tissue, in addition to an energy storage house is an endocrine organ that secretes various adipokines. The other member of this cytokine family includes adiponectin, leptin, Resistin and PAI-1. Adiponectin is a potent insulin sensitizer. In obese patients who are allied with insulin resistance, various signalling pathways get activated which are implicated to regulate metabolism because of down regulation of adiponectin and its receptors [67]. AdipoRs (Adiponectin receptors) are mainly involved in AMPK and PPAR-α ligand activity. AMPK affects glucose uptake and β-oxidation by Adiponectin [68]. Binding and actions of adiponectin are blocked by both AdipoR1 and AdipoR2, leading to insulin resistance [69].

Leptin

The adipocytokine originates from a Greek word 'LEPTOS' that means thin. Leptin is responsible for providing normal insulin sensitivity. There is an increase of leptin in obesity and decrease during fasting, because leptin levels are correlated with energy stores. Decreased level of leptin during fasting effect various hormones that includes growth, thyroid and reproductive hormones by causing its suppression [70]. Leptin stimulates appetite and inhibits activity of sympathetic nerves. Moreover, distorted adipose tissue have been reported in case of severe insulin resistant diabetes in hyperphagic mice. Leptin present in circulation crosses blood brain barrier that acts via a JAK-STAT3 pathway [71]. Leptin is considered as the "fat-burning" hormone that has opposing effect of insulin, the "fat-promoting" hormone. It lowers the intake of food and raises expenditure of energy and hence, insulin sensitivity [67].

FFA and tumor necrosis factor α

In recent years, the prospect for insulin resistance switched from 'glucocentric' to 'lipocentric'. As obesity and type 2 diabetes are correlated with plasma free fatty acids [72]. Thus, insulin resistance and type 2 diabetic patients correlated with assembly of lipids in hepatocytes and myocytes that has also been observed in non-diabetic offspring of type 2 diabetic subjects [73]. In obesity, TNF-α is released from adipose in large amount that further stimulates adipose tissue to release free fatty acids thus act as a player for causing IR. The underline mechanism involved in insulin resistance include elevated fatty acids, which raises ratios of mitochondrial NADH: NAD+ and Acetyl CoA: CoA along with enzyme pyruvate dehydrogenase inactivation. This further elevates citrate concentrations, leading to functional alteration in phosphofructokinase (a rate limiting enzyme in glycolysis) that causes assembly of glucose-6 phosphate thus halting hexokinase II activity consequently increases glucose concentration intracellularly with lowered glucose uptake [74].

Other adipokines

Other adipokines include MCP-1, PAI-1, IL-1 and IL-10. MCP-1 (secreted by adipocytes) causes IR as per the observation made using cultured adipocyte that has shown alteration in glucose uptake and insulin receptor's Tyr phosphorylation. MCP-1engages macrophages to adipose tissue and recommend the release of IL-1 and TNF-α. However, PAI-1 expression is found in abundance in visceral than subcutaneous adipose tissue [75].

Glucocorticoids and FFA

Glucocorticoids stimulates liver gluconeogenesis thus raises FFA level, which in turn causes decreased glucose oxidation and hence the peripheral uptake of glucose in tissue. The possible ways for increased lipolysis by glucocorticoids is - a) phenyl-ethanolamine N-methyltransferase enzyme catalyses noradrenaline transformation to adrenaline, which is raised by glucocorticoids. Adrenaline by acting on lipase increases lipolysis in adipose tissue b) inhibition of lipoprotein lipase that inhibit FFA transport in adipose tissue c) directly gear up regulation of hormone-sensitive lipase d) Signal transduction defects in insulin action (IR/IRS-I/PI 3-kinase/PKCζ/λ/Akt pathway)- binding of insulin to α subunits mainspring autophosphorylation of tyrosine residue. As an outcome, there is translocation of insulin receptor substrate (IRS) -1 and binding to p85 (Phosphatidyl (PI) -3-kinase (PI3-K) subunit), which paramount to PI-3K activate. Further, step to step mechanism is shown in figure 5.

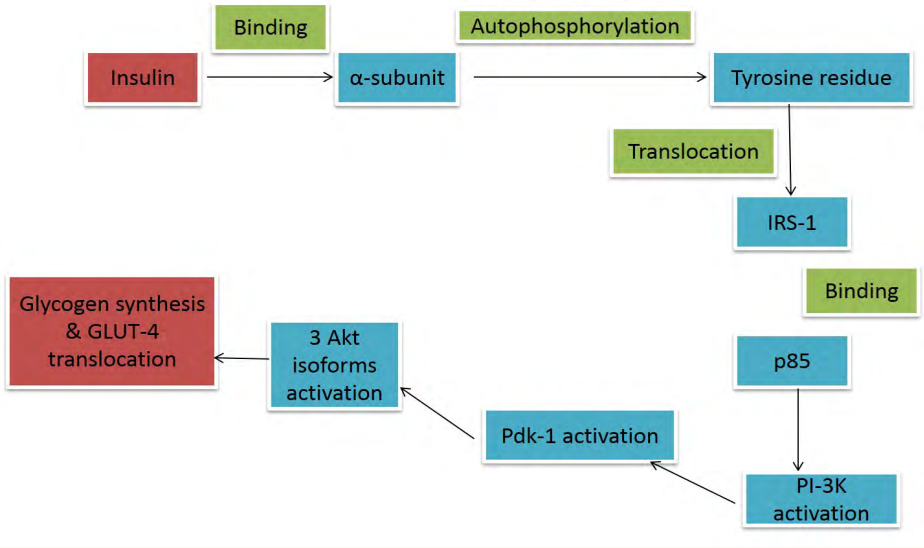

Figure 5: *IR/IRS-1/PI-3 Kinase/PKCζ/λ/Akt Pathway.*

Markers of IR

Neuroendocrine peptides- Galanin and GALP

Galanin

Galanin is a 29/30 amino acid peptide. The expression of galanin and its receptors is found in both peripheral and central nervous system along with in other tissues (like liver, skeletal and adipose tissue) [76]. In islets, galanin coexist with insulin, which results in interaction between them. Galanin receptors are of three types- GalR1, GalR2 and GalR3. The galanin acts as biomarker for insulin resistance as- a) It promotes food intake, body weight and adiposity, b) type 2 diabetes is more prevalent in metabolic disorder of galanin in animals, c) Galanin gene knockout mice showed disrupted disposal of glucose because of decreased insulin response, d) In type 2 diabetic animals, galanin have shown to increase sensitivity of insulin by raising expression and translocation of GLUT4 in myocytes and adipocytes [77-79]. This demonstrates association of insulin sensitivity with glucose level in blood.

GALP

GALP (Galanin-like peptides) is a neuropeptide having 60 amino acids. It activates all three galanin Receptors (GalR-1-3). The central injection of GALP, increases GLUT mRNA expression levels, uptake of glucose and lipid metabolism, but inhibit glucose formation and synthesis of fatty acid in mice [80]. In STZ-induced diabetic rats, the expression of GALP mRNA level is found to get lower in hypothalamus and arcuate nucleus which can be reverted back through peripheral administration of insulin.

Non-neuroendocrine peptides

Ghrelin

Ghrelin is a gut-brain peptide having 28 amino acids that produces central orexigenic effects. Ghrelin circulates in two forms- acylated (A-Ghr) and deacylated (D-Ghr). Total ghrelin level in plasma is reduced in obesity or after diet-induced weight gain. Centrally or peripheral injected ghrelin potentially stimulates food intake [81]. Ghrelin act as biomarker for insulin resistance. Correlation between ghrelin levels and occurrence of insulin resistance is beneficial [82].

Adiponectin

Adiponectin is a hormone having 244 amino acids which is found in skeletal muscle, liver and pancreatic islet tissue. Adiponectin receptors are classified into three- 1, 2 and T-Cadherin [83]. There is a positive relationship between adiponectin level in plasma and high density lipoprotein levels. Insulin signalling pathway is found to be defective in adiponectin gene knockout mice, as IRS-1, IRS-2 is decreased [84]. In addition, *in vitro* experiments show activation of phosphoinositide 3 kinase, that increases glucose metabolism in muscle cells. It can be concluded that adiponectin can be used as a negative marker to detect insulin resistance.

Retinol-binding protein 4

Retinol binding protein 4 (RBP4) is a 181 amino acid. The adipokine- ABP4 is recently described to partly responsible for insulin resistance. Levels of RBP4 levels are positively in relationship with insulin resistance severity [85]. In diabetic patients, expression of RBP4 is found to be decreased in adipocytes; metformin improves total insulin sensitivity [71]. GLUT-4 gene knockout mice possess an increased level of plasma RBP4 and hence observed as insulin resistant. The high levels of RBP4 lead to insulin resistance, suggesting RBP4 as a clinical predictor for identifying insulin resistance [71].

C-Reactive Protein (C-RP)

It is pentameric protein, levels of which get increased in response to inflammation [86]. C-RP increases phagocytosis, increased macrophages synthesis, lymphocytes. Also, causes an increase in triglyceride and fasting glucose levels, suggesting a relation of C-RP and insulin resistance. C-RP and insulin resistance are directly related to each other. Thus, this can be considered as insulin resistance marker [86].

Insulin resistance in central nervous system

Recent studies have shown that impaired insulin signalling or insulin resistance is termed as 'type-3 diabetes' or AD 'an insulin resistant brain state'.

The insulin resistance and Aβ metabolism are related in a compelling manner and is in relevance to AD. There is reduced insulin receptor activity in brain with AD disease [87] along with lower CSF insulin levels and hyperinsulinemia in periphery [88]. Due to disrupted insulin signalling in brain, there is additional contribution to memory loss in AD disease and insulin resistance as well [89].

Also, amyloid beta and glycogen synthase kinase-3 beta synaptic loss of hippocampal neurons is alleviated by Insulin, thereby phosphorylation of tau protein is inhibited. Tau protein forms fibrillary tangles which is pathological feature of AD [90] (Figure 6).

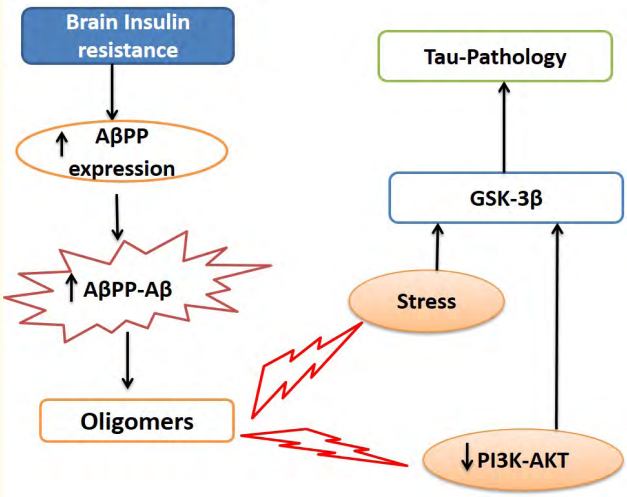

Figure 6: *Insulin resistance in Alzheimer's disease Pathology.*

The processing of AβPP and clearance of Aβ is disturbed by impairment of insulin signalling [91]. Aβ further disrupts insulin signalling by competing with insulin or reducing its affinity to bind with its own receptor.

In addition to this, chronic inflammation has been found to be a common platform to contribute to risk for insulin resistance and memory loss in AD [89,92]. The Aβ (misfolded soluble) has been reported to induce inflammatory cytokines (TNF-α) through NIK- dependent pathway [93]. This suggest the role of Aβ to insulin resistance in brain [94-96].

Summary and Conclusion

The present review summarises the aetiology, pathogenesis and pathophysiology involved in insulin resistance. The aetiology of insulin resistance (IR) involves genetic factors as well as environmental factors. The pathophysiological hallmarks of insulin resistance include deregulation of free fatty acid, adipokine secretion, glucocorticoids and regulation of glucose transport. The distinctive features in pathogenesis involve ectopic lipid accumulation, inflammation, oxidative stress, sleep deprivation and production of advanced glycated end products. The author concludes that ectopic lipid accumulation (free fatty acid accumulation) and oxidative stress are major hallmarks in the development of insulin resistance. There are some recent advances showing pathogenic involvement in insulin resistance like microRNAs, histone deacetylase, and toll like receptors, microbiota and short chain fatty acids. The recent advances in explaining the role of insulin resistance in brain has also summarised and that plays a crucial role in AD patients. In fact, the insulin resistance occurring

in brain in AD patients is termed as type 3 diabetes. Although, the studies have shown their involvement in insulin resistance but the exact pathophysiological pathway is an ongoing research. There can be various possible drug targets for future research which can show promising results in the cure of insulin resistance.

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