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Physiology of Insulin Resistance and Its Relationship with the Central Nervous System: An Advanced Review

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ABSTRACT

Autism Insulin resistance (IR) is a multifaceted metabolic condition characterized by diminished cellular sensitivity to insulin, resulting in compromised glucose absorption, increased insulin concentrations, and eventually leading to type 2 diabetes and cardiovascular problems. The conventional perspective of insulin resistance as a peripheral disorder impacting muscle, liver, and adipose tissue has been supplanted by new discoveries indicating that the central nervous system (CNS), especially the hypothalamus, is crucial in starting and regulating systemic insulin sensitivity. Insulin serves as a metabolic hormone and a neuroregulatory signal that regulates hunger, energy expenditure, and peripheral glucose homeostasis via complex brain circuits.

This review delivers an advanced and comprehensive analysis of insulin resistance mechanisms with emphasis on CNS involvement. The review investigates how central insulin signaling pathways together with blood-brain barrier insulin transport and hypothalamic inflammation and neuronal insulin resistance create systemic metabolic problems. The article investigates how central insulin resistance affects both neurodegenerative diseases like Alzheimer's disease and mood disorders including depression. The article examines current therapeutic strategies which focus on the brain–insulin axis.

INTRODUCTION

DEFINITION AND CLINICAL SIGNIFICANCE OF INSULIN RESISTANCE

The biological response of skeletal muscle and adipose tissue and liver to normal or elevated insulin levels becomes diminished in insulin resistance (IR). The body uses insulin to enable muscle cells and fat cells to absorb glucose while simultaneously reducing liver glucose production which helps maintain normal blood sugar levels. The impaired processes in insulin resistance trigger pancreatic β-cells to produce more insulin which results in hyperinsulinemia [1].

Insulin resistance functions as the primary clinical marker for multiple metabolic disorders including type 2 diabetes mellitus (T2DM) and obesity and metabolic syndrome and non-alcoholic fatty liver disease (NAFLD) and polycystic ovary syndrome (PCOS). The condition leads to elevated cardiovascular risks as well as systemic inflammation and damage to blood vessel linings [2]. The onset of overt hyperglycemia occurs after several years of insulin resistance development which makes it an essential preventive target for metabolic health. The persistent high insulin levels from IR create separate pathophysiological effects that include increased sympathetic nervous system activity and sodium retention and mitogenic effects which may lead to hypertension and specific cancers [3].

HISTORICAL PERSPECTIVE ON PERIPHERAL VS. CENTRAL INSULIN ACTION

Scientific understanding of insulin resistance has predominantly centered on peripheral tissues over several decades. The preliminary research investigations focused on skeletal muscle due to its primary role in postprandial glucose absorption and its significance as the principal site of insulin resistance. Investigations into insulin receptor anomalies, with post-receptor signaling deficiencies (including compromised IRS-1/PI3K/Akt pathways) and GLUT4 translocation failures, elucidated the molecular underpinnings of peripheral insulin resistance. Researchers investigated hepatic insulin resistance concurrently to comprehend its impact on gluconeogenesis and fasting blood glucose levels [4],[5].

The identification of hypothalamic insulin receptors and the controlled translocation of insulin over the blood-brain barrier has fundamentally altered our understanding. Research undertaken in the late 20th century demonstrated that insulin significantly influences food behavior, energy expenditure, and neuroendocrine functioning. Research on neuron-specific insulin receptor knockouts in animal models revealed that the brain plays an active role in regulating systemic glucose metabolism [6].

The distinction between peripheral and central insulin action currently seems to be an antiquated notion in scientific comprehension. Contemporary studies indicate that insulin resistance operates as a complex mechanism involving ongoing interaction between peripheral tissues and the central nervous system (CNS). The brain identifies peripheral metabolic signals and employs autonomic, neuroendocrine, and behavioral systems to regulate insulin sensitivity from a higher level [7].

OBJECTIVE AND SCOPE OF THE REVIEW

The main goal of this review is to provide a mechanistic and comprehensive

understanding of insulin resistance with a special focus on its relationship with the central nervous system. This article aims to integrate recent advances that show the CNS as both a regulator and a target of insulin action while acknowledging the well-established peripheral aspects of IR. The article focuses on hypothalamic regulation, blood-brain barrier transport of insulin, neuronal insulin signaling, and the role of neuroinflammation in impairing central insulin sensitivity.

DISCUSSION

PHYSIOLOGY OF INSULIN AND ITS CLASSICAL ACTIONS

OVERVIEW OF INSULIN SYNTHESIS AND SECRETION

Insulin acts as a peptide hormone solely produced by the β-cells of the Langerhans islets in the pancreas. The pancreas produces preproinsulin as a single-chain precursor molecule which serves as the initial form of insulin production. The endoplasmic reticulum removes the signal peptide from preproinsulin to produce proinsulin. The molecule then undergoes structural changes through disulfide bond formation before it moves to the Golgi apparatus for packaging into secretory granules [8].

Endopeptidases prohormone convertase 1/3 and 2 cleave proinsulin within secretory granules, producing insulin and C-peptide, which are released into the bloodstream in equivalent amounts following glucose stimulation. Blood glucose levels serve as the primary control of insulin secretion. The GLUT2 transporter enables glucose access into β-cells, which then metabolize it by glycolysis and oxidative phosphorylation, hence increasing the ATP/ADP ratio. The elevated ATP/ADP ratio prompts the closure of ATP-sensitive potassium (K_ATP) channels, leading to membrane depolarization and the activation of voltage-gated calcium channels. The entry of calcium ions into the cell triggers the exocytotic secretion of insulin-containing granules [9],[10].

The insulin release process has two phases: an initial rapid release of stored insulin, succeeded by a longer phase that integrates fresh insulin synthesis with further granule release. The secretion of insulin from β-cells is contingent upon glucose, incretin hormones (GLP-1, GIP), amino acids, fatty acids, autonomic innervation, and circulating hormones, including glucagon (Figure 1) [11].

INSULIN SIGNALING PATHWAYS (PI3K-AKT, MAPK)

Insulin acts on target cells through its receptor (IR), a transmembrane tyrosine kinase present on virtually all cell surfaces, e.g., especially the liver, muscle, and fat. The insulin receptor is also a heterotetrametric, with two extracellular alpha subunits and two transmembrane beta subunits. Insulin binding to the receptor results in autophosphorylation of the β-subunits on tyrosine residues and activation of a signaling pathway [12].

This results in the activation of primarily two signaling cascades (Figure 2): (1) the PI3K-Akt and (2) the MAPK pathways. The PI3K-Akt pathway is the major metabolic branch of insulin activity. It starts with insulin receptor substrates (IRS-1 and IRS-2) phosphorylation on tyrosine residues, allowing them to bind with p85 regulatory subunit of PI3K. Activation of PI3K hydrolyzes PIP2 to PIP3, allowing recruitment and activation of PDK1 and Akt (protein kinase B) [13].

Upon activation, Akt has various metabolic downstream effects such as the transport of

GLUT4 to the plasma membrane due to glucose uptake in adipose and muscle cells, the repression of glycogen synthase kinase 3 (GSK3) to stimulate glycogen synthesis, and the inhibition of FOXO1 resulting in the decreased hepatic gluconeogenesis as well as the control of lipid metabolism, the latter being either promotion of lipogenesis, or the repression of lipolysis [14]. On the other side, the MAPK pathway, activation of which occurs through adaptor proteins as Grb2 and SOS (also known as the Ras/Raf/MEK/ERK cascade), is more related to controlling cell growth, survival, and differentiation than with immediate metabolic reactions [15].

The regulation of the two pathways is extremely important for the normal physiological action of insulin. On the other hand, the PI3K-Akt pathway is quite impaired in insulin resistance, but the MAPK pathway is still active. This dysregulation not only impairs the metabolic action, but also exposes to permissive mitogenic signaling, also associated to enhance the cardiovascular risk [16].

PERIPHERAL TARGET TISSUES:

MUSCLE, LIVER, AND ADIPOSE

TISSUE

The three peripheral tissues of skeletal muscle liver and adipose tissue (Figure 3) serve as the primary locations where insulin performs its classical functions to regulate glucose and lipid homeostasis throughout the body [17].

Skeletal muscle cells absorb approximately 70–80% of the glucose that enters the body after eating in people with normal glucose metabolism. Insulin enables muscle cells to take in glucose through GLUT4 translocation while simultaneously activating glycogen synthase for glycogen synthesis and blocking proteolytic processes. The impaired GLUT4 translocation in insulin resistance leads to reduced glucose uptake which results in elevated blood sugar levels [18].

The liver responds to insulin by reducing its production of glucose through suppression of gluconeogenesis and glycogenolysis. The hormone promotes both glycogen accumulation and new lipid formation. The process is mainly controlled through FOXO1 inhibition and SREBP-1c (Sterol regulatory element-binding protein 1c) activation. The inability of hepatic insulin signaling to reduce gluconeogenesis in insulin-resistant states results in higher fasting blood glucose levels [19].

The insulin hormone reduces lipolysis by blocking hormone-sensitive lipase (HSL) and stimulates lipid storage through the activation of lipogenic enzymes. The activation of GLUT4 in adipocytes enables glucose uptake that results in glycerol-3-phosphate production which supports triglyceride synthesis. The resistance of adipose tissue to insulin results in elevated free fatty acid release that worsens ectopic fat accumulation and reduces insulin sensitivity across other body tissues [20].

The peripheral tissues maintain glucose and lipid metabolism through insulin's tightly coordinated actions. Any disruption in insulin synthesis or secretion or downstream signaling will trigger a sequence of metabolic abnormalities. The classical pathways of insulin function provide essential knowledge to study how insulin operates in the central nervous system and its brain resistance effects on systemic body function which is discussed in the following sections [21].

MECHANISMS OF PERIPHERAL INSULIN RESISTANCE

The development of peripheral insulin resistance is attributable to several molecular, cellular, and systemic factors that impair insulin signaling pathways and disturb normal glucose and lipid metabolism. The development of insulin resistance is influenced by hereditary variables; however, environmental and lifestyle influences such as overnutrition, physical inactivity, and chronic low-grade inflammation are the most significant contributors [22]. This section analyses the processes of peripheral insulin resistance via serine phosphorylation of signaling molecules, the role of SOCS proteins, and the impacts of obesity, lipotoxicity, inflammation, and oxidative stress.

MOLECULAR MECHANISMS (SERINE PHOSPHORYLATION, SOCS PROTEINS, ETC.)

At the molecular level, the central mechanism responsible for peripheral insulin resistance are defects in the insulin signaling pathway downstream from the insulin receptor activation. This defect is due to inappropriate serine/threonine phosphorylation of insulin receptor substrates, such as IRS-1 and IRS-2 as opposed to the normal process in which insulin binding activates tyrosine phosphorylation. This tyrosine phosphorylation is required for PI3K recruitment and activation of the Akt signaling pathway. In conditions of insulin resistance, on the other hand, several kinases, including JNK (c-Jun N-terminal kinase), IKKβ (IκB kinase beta), PKC (Protein Kinase C), and S6K1 (ribosomal protein S6 kinase 1), are induced and phosphorylate IRS proteins on specific serine sites [23],[24].

This abnormal modification disrupts PI3K interaction, resulting in attenuation of Akt signaling, inhibition of GLUT4 cell surface translocation, and ultimately reduced cellular glucose uptake. Induratory diseases also result in elevations of SOCS proteins and two of these, SOCS-1 and -3, is commonly upregulated in inflammation (Figure 4) [37]. These proteins further interact with insulin receptors and IRS molecules, inducing them to undergo ubiquitination and be degraded by the proteasome. As a consequence, the function of the insulin signaling is dramatically impaired resulting in decreased metabolic response. In general, a number of molecular alterations affect signaling networks indispensable for glucose and lipid homeostasis [25],[26].

Lipotoxicity, defined by an irregular buildup of lipid intermediates in liver and skeletal muscle tissues, is a significant factor in peripheral insulin resistance associated with central or visceral obesity. The body typically stores surplus energy via triglyceride buildup in adipose tissue [27]. The storage capacity of adipose tissue is surpassed when individuals have persistent caloric surplus, resulting in the hypertrophy of fat cells. The body accumulates hazardous lipid species, such as diacylglycerols (DAGs) and ceramides, in atypical fat storage sites, hence disrupting insulin signaling pathways [28]. The activation of PKCθ novel isoforms by DAGs in skeletal muscle results in IRS-1 serine phosphorylation which blocks insulin action. The inhibition of Akt phosphorylation by ceramides disrupts GLUT4 translocation and glucose uptake processes. PKCε activation by DAGs in the liver causes impaired suppression of gluconeogenesis which represents a fundamental insulin function [29]. Obesity causes adipose tissue to

develop metabolic issues which result in elevated free fatty acid (FFA) and pro-inflammatory adipokine production while simultaneously decreasing adiponectin hormone levels that enhance insulin sensitivity (Figure 5). The elevated FFAs serve as lipotoxicity substrates for other tissues while generating systemic inflammation and oxidative stress which intensifies insulin resistance [30].

INFLAMMATION AND OXIDATIVE STRESS

Research findings show that insulin resistance develops as a result of persistent low-grade inflammation. The immune cells M1-polarized macrophages infiltrate adipose tissue in obesity to produce pro-inflammatory cytokines TNF-α, IL-6 and MCP-1 [31]. The cytokines activate stress kinases JNK and IKKβ inside cells which then modify IRS proteins through serine phosphorylation to disrupt insulin signal transmission. The inflammatory cytokines lead to SOCS protein activation which results in impaired insulin receptor function. The inflammatory process becomes more severe because free fatty acids activate pattern recognition receptors TLR4 (Toll-like receptor 4) on macrophages and adipocytes to initiate NF-κB-mediated transcription of pro-inflammatory genes [32].

The development of insulin resistance depends heavily on oxidative stress which occurs simultaneously with inflammation (Figure 6). The excessive production of reactive oxygen species (ROS) by mitochondria under conditions of nutrient overload leads to cellular damage while activating redox-sensitive kinases including p38 MAPK and JNK. The accumulation of lipids and protein misfolding activates endoplasmic reticulum (ER) stress which leads to unfolded protein response (UPR) activation and increased expression of stress molecules CHOP and XBP1 that both promote inflammation and impair insulin signaling. The harmful cellular environment which develops from inflammation and oxidative stress and ER dysfunction maintains insulin resistance throughout peripheral tissues [33],[34].

THE CENTRAL NERVOUS SYSTEM AND METABOLIC REGULATION

CENTRAL INSULIN SIGNALING:

BRAIN INSULIN RECEPTORS AND NEURONAL PATHWAYS

Several recent studies have confirmed insulin's well-known role in peripheral glucose control, and more importantly, they have emphasized the central nervous system, particularly the hypothalamus. The CNS regulates overall energy balance and glucose homeostasis. The blood brain barrier allows insulin to penetrate through a receptor-mediated transport mechanism. Insulin's primary targets are the brain's insulin receptors that are dispersed, but particularly found in the hypothalamus, hippocampus, and cerebral cortex at high levels [35].

There are insulin receptors overexpressed within the hypothalamus, especially in the arcuate nucleus, ventromedial hypothalamus (Figure 7), and paraventricular nucleus. Once bound by insulin, the insulin receptor starts intracellular signaling cascades, such as the PI3K-Akt and MAPK pathways. These pathways mimic the way insulin acts in addition to peripheral tissues. In the hypothalamus, insulin signaling through POMC neurons increases melanocortin signaling, which also suppresses appetite and increases energy expenditure [36].

At the identical time, insulin signaling through the melanocortin receptors inhibits NPY and AGRP-expressing neurons, which are proven to increase food consumption and metabolic rate. Apart from controlling the local brain activity, brain insulin signaling also has a broad effect on metabolism through the brain-liver axis. The CNS also has substantial control over autonomic outputs from the autonomic nervous system and the vagal efferent pathway autonomous of circulating insulin through the brain-liver axis. Through this complex neuroendocrine system, the brain appears to be an active player in systemic insulin sensitivity and metabolic function [37].

HYPOTHALAMIC REGULATION OF APPETITE, ENERGY BALANCE, AND GLUCOSE HOMEOSTASIS

The hypothalamus serves as the main center that integrates metabolic information from hormones (such as insulin, leptin, ghrelin) and nutrients (like glucose, fatty acids) and neural signals (Figure 8). The hypothalamic neurons integrate these signals to control food consumption and body heat production and blood sugar management. The neuroendocrine regulation depends heavily on insulin which works together with leptin to provide the brain with information about body energy status [38].

The postprandial increase in insulin levels triggers satiety signals through POMC neuron activation and NPY/AgRP neuron suppression. Insulin regulates short-term appetite reduction and long-term energy homeostasis through these mechanisms. Insulin controls the sympathetic and parasympathetic outputs which affect liver glucose production and adipose tissue lipolysis. Experimental studies show that CNS insulin administration directly reduces HGP and enhances peripheral insulin sensitivity without altering systemic insulin concentrations [39].

The hypothalamus develops reduced sensitivity to insulin when central insulin resistance occurs together with obesity and inflammation. The condition leads to excessive food consumption and reduced energy expenditure and impaired control of hepatic glucose production which together create the pathophysiological mechanisms of systemic IR [40].

The blood-brain barrier (BBB) is a selective permeable barrier between the blood and the brain. In view of the close junctions and structural integrity of the BBB, insulin is unable to diffuse passively through the BBB; its transport depends on the insulin receptors on the brain endothelial cells for receptor-mediated transcytosis. Within the CNS, insulin interacts with both neurons and glial cells through binding to saturable receptors in controlling functions [41].

Insulin transport across the BBB (Figure 9) is compromised, however, under conditions such as obesity and type 2 diabetes resulting in a state of central insulin-deficiency despite of high peripheral insulin levels. This disconnection results in the evolution of central insulin resistance by which the normal dialogue between the brain and peripheral metabolic quarters is rendered inoperative. Moreover, the chronic inflammation and oxidative stress developed within the context of metabolic disorders, may undermine the integrity of the BBB and counteract insulin access to the brain, contributing in the aggravation of centrally-driven metabolic disarrangement [42].

Research demonstrates that administering insulin directly to the central nervous system by intranasal delivery benefits

individuals with insulin resistance, Alzheimer's disease, and type 2 diabetes by improving cognitive function and metabolic health. The BBB operates as an active regulator of insulin's central effects rather than only serving as a physical barrier [43],[44].

CENTRAL IR: MECHANISMS AND METABOLIC CONSEQUENCES

DEFINITION AND EVIDENCE FOR CENTRAL INSULIN RESISTANCE

The pathological condition of central insulin resistance (CIR) occurs when the brain specifically the hypothalamus fails to respond to insulin even when systemic insulin levels remain normal or elevated. The brain's regulatory functions for feeding behavior and energy expenditure and hepatic glucose output become impaired in CIR whereas peripheral insulin resistance primarily affects muscle and adipose tissue glucose uptake [45].

Research evidence supporting CIR exists through both animal-based and human-based investigations. Research using rodent models demonstrates that brain-administered insulin decreases both food consumption and liver glucose production through hypothalamic signaling pathways. The development of obesity through high-fat diet consumption damages insulin signaling pathways in hypothalamic neurons which results in reduced insulin receptor and IRS-1 and Akt phosphorylation. Functional neuroimaging studies using intranasal insulin reveal that insulin-resistant and obese individuals show reduced brain activity in areas that control appetite and reward processing including the prefrontal cortex and hypothalamus. The medical community now understands CIR as both a result of metabolic disorders and a key factor that maintains obesity and type 2 diabetes and potentially neurodegenerative diseases [46],[47].

CELLULAR AND MOLECULAR MECHANISMS (INFLAMMATION, ER STRESS, IMPAIRED SIGNALING)

The cellular mechanisms for central insulin resistance (CIR) in the central nervous system are analogous to those in the periphery, but take place in the additional context of the physiological brain. Especially the arcuate nucleus and medio basal hypothalamus (MBH) are mainly targeted for hypothalamic inflammation. During a state of overnutrition, particularly when the food consumed is high in saturated fats, microglial and astrocytes are activated with release of proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6). These cytokines, in turn, activate intracellular stress signaling pathways (including JNK, IKKβ, and NF-κB) in hypothalamic neurons that cause serine phosphorylation of insulin receptor substrates and thus, blockade of insulin signal transduction [48].

Concomitantly to this inflammatory response, nutrient surplus also leads to oxidative stress, which in turn triggers ER-stress mechanisms. The UPR that is activated to restore ER homeostasis becomes dysregulated under chronic stress, and impairs insulin receptor traffick and signaling. Increased expression of UPR-related factors such as CHOP, XBP1, and ATF4 inhibit neuronal insulin signaling, and under more severe conditions, they can lead to intracellular dysfunction or apoptosis [49].

The development of leptin resistance stands as a vital factor because it commonly appears together with CIR. The brain's ability to detect adiposity signals

becomes impaired when resistance to one hormone leads to resistance of the other hormone because insulin and leptin share common intracellular pathways (PI3K-Akt, STAT3) which results in uncontrolled energy intake and decreased energy expenditure [50].

The impaired mitochondrial function in hypothalamic neurons leads to reduced ATP production which disrupts insulin receptor recycling and increases reactive oxygen species (ROS) to create a pro-inflammatory and insulin-resistant state [51].

IMPACT ON PERIPHERAL GLUCOSE HOMEOSTASIS, APPETITE, AND ENERGY EXPENDITURE

The central insulin resistance produces extensive effects which affect various peripheral metabolic processes. The brain-liver axis experiences disruption because central insulin normally uses parasympathetic signals to suppress hepatic glucose production (HGP). The loss of inhibitory signals in CIR results in inappropriate gluconeogenesis that occurs during the postprandial state and directly causes fasting hyperglycemia [52].

CIR impairs the brain's capacity to regulate food intake effectively. The postprandial insulin signal typically operates in the brain to diminish hunger by stimulating POMC/CART neurons and inhibiting NPY/AgRP neurons in the arcuate nucleus. The insulin-resistant hypothalamus exhibits diminished signaling from postprandial insulin, resulting in heightened food intake, a predilection for high-calorie meals, and worse control of satiety. The situation engenders a detrimental cycle of overeating that results in weight gain and exacerbated insulin resistance [53].

The brain uses insulin to increase energy expenditure through its effects on the sympathetic nervous system (SNS) and brown adipose tissue thermogenesis and physical activity regulation. The metabolic processes controlled by CIR become impaired which leads to energy storage and fat accumulation. The central insulin resistance functions as both an initial cause and an intensifying factor for systemic metabolic disease which connects brain problems to blood sugar control issues and obesity and energy imbalance [54].

CENTRAL INSULIN RESISTANCE AND NEURODEGENERATIVE DISEASES

LINK BETWEEN CENTRAL IR AND AD

Cerebral insulin resistance (CIR) has been increasingly studied due to the major role it plays in the pathogenesis and evolution of neurodegenerative diseases, especially Alzheimer's disease (AD). Commonly referred to as "type 3 diabetes", Alzheimer's has common metabolic dysfunctions with type 2 diabetes, namely disrupted insulin-sensitive signaling cascade in the brain. Insulin has important functions in CNS, assisting in neuron survival, synaptic plasticity and cognitive processes (learning and memory) [55].

The intracellular signaling pathways PI3K-Akt and MAPK mostly mediate these activities. The neuroprotective mechanisms enabled by these pathways are compromised when CIR interferes with their functioning. Neurones demonstrate heightened vulnerability to oxidative stress, mitochondrial dysfunction, and synaptic disconnection, which are preliminary signs of Alzheimer's disease pathology [56].

The normal metabolism of amyloid precursor protein (APP) is altered when insulin signaling is compromised, leading to the excessive accumulation of amyloid-

beta (Aβ) plaques, a principal pathological characteristic of Alzheimer's disease. Insulin often facilitates Aβ breakdown by activating insulin-degrading enzyme (IDE). The brain undergoes inadequate clearance of Aβ aggregates due to diminished IDE activity in CIR circumstances, resulting in the accumulation of harmful Aβ aggregates. CIR exacerbates both amyloid and tau protein abnormalities, among its other effects [57].

The phosphorylation of tau proteins and the development of neurofibrillary tangles intensify due to the inhibition of GSK3β activity by insulin signaling via Akt. The synergistic impact of amyloid plaque buildup and tau hyperphosphorylation leads to increasing neuronal malfunction and cognitive impairment, hence initiating the neurodegenerative cascade in Alzheimer's disease [58].

MECHANISMS LINKING METABOLIC DYSFUNCTION TO COGNITIVE DECLINE

The central insulin resistance produces cognitive impairment by affecting brain homeostasis through various mechanisms which extend beyond its direct impact on amyloid and tau pathology. Chronic neuroinflammation stands as a major factor which contributes to this condition. The activation of microglia and astrocytes in hypothalamic and cortical regions of insulin-resistant states produces prolonged release of pro-inflammatory cytokines [59]. The inflammatory environment damages neurons while disrupting synaptic signals which results in impaired cognitive performance. The brain cells known as neurons depend mainly on glucose for their energy requirements. The impaired glucose metabolism in neuronal cells caused by CIR leads to energy deficits which damage synaptic function and neuroplasticity essential for memory and learning processes [60].

Insulin resistance creates vascular problems that affect the brain's blood vessels. Endothelial dysfunction causes decreased cerebral blood flow that restricts oxygen and nutrient delivery while making it difficult to remove metabolic waste products. The insufficient blood supply of the brain worsens both neuronal stress and cognitive deterioration. The progression of cognitive impairment due to CIR depends heavily on mitochondrial dysfunction and oxidative stress as its fundamental factors. The elevated production of ROS damages both mitochondrial DNA and proteins which triggers apoptotic signals that result in neuronal death. The neurodegenerative environment develops through the combined effects of these pathological processes which speed up memory impairment and dementia progression [61],[62].

THERAPEUTIC IMPLICATIONS: TARGETING CENTRAL INSULIN RESISTANCE IN NEURODEGENERATION

The identification of central insulin resistance as a core pathological mechanism in neurodegenerative diseases has prompted the creation of novel treatment approaches aimed at enhancing brain insulin sensitivity. Intranasal insulin administration is a promising therapeutic approach as it traverses the blood-brain barrier to activate insulin signaling pathways inside the central nervous system [63]. Research experiments indicate that intranasal insulin treatment enhances memory outcomes and cognitive function in individuals with moderate cognitive

impairment and early-stage Alzheimer's disease, hence offering potential therapeutic advantages. Neurodegenerative progression and insulin resistance can be mitigated by targeting inflammatory processes in the hypothalamus and cortex with NSAIDs, PPAR agonists, and novel neuroimmune modulators [64].

Research continues to develop pharmacological agents that enhance mitochondrial function and reduce endoplasmic reticulum stress because these agents promote neuronal well-being and strengthen insulin signaling pathways. The combination of dietary changes and physical exercise serves as essential lifestyle interventions which enhance both body-wide insulin sensitivity and brain health while promoting cognitive function. Researchers are developing new therapeutic approaches which investigate molecules that improve blood-brain barrier insulin transport and neuron insulin receptor sensitization for more precise and powerful treatments.

These therapeutic methods simultaneously reduce systemic metabolic problems and defend the brain from neurodegenerative progression by treating central insulin resistance. The integrated treatment approach demonstrates that metabolic health stands as an essential foundation for preventing and treating cognitive decline and Alzheimer's disease [65],[66].

CNS INSULIN RESISTANCE IN SYSTEMIC METABOLIC DYSREGULATION

FEEDBACK LOOPS BETWEEN CENTRAL AND PERIPHERAL INSULIN RESISTANCE

The blood-brain barrier (BBB) allows insulin to pass through by receptor-mediated transport which enables the regulation of neurons that control peripheral metabolic functions [67]. The hypothalamus receives insulin signals which control hepatic glucose production and regulates autonomic nervous system outputs to adipose tissue and muscle and affects both feeding behavior and energy expenditure. The homeostatic control system becomes disrupted when CNS insulin resistance develops which results in impaired hepatic gluconeogenesis suppression and reduced peripheral glucose uptake and dysregulated lipid metabolism [68],[69].

The main characteristic of this dysfunction involves the creation of harmful feedback mechanisms between central and peripheral insulin resistance. The body develops peripheral insulin resistance when muscle cells and liver cells and adipose tissue fail to respond adequately to insulin which produces elevated blood glucose and insulin levels and increased free fatty acids (FFAs) [70]. The metabolic problems create obstacles for insulin transport across the blood-brain barrier while simultaneously reducing central insulin signaling which worsens CNS insulin resistance. The brain's insulin resistance leads to peripheral insulin resistance through neuroendocrine output dysregulation which results in increased sympathetic nervous system activity that produces systemic inflammation and ectopic fat accumulation. The mutual relationship between these conditions forms a self-reinforcing cycle which worsens metabolic problems and makes disease progression more challenging [71].

ROLE IN OBESITY, TYPE 2 DIABETES, AND METABOLIC SYNDROME

CNS insulin resistance functions as a fundamental factor that leads to the creation and worsening of obesity. The hypothalamus functions as a central hub that processes signals about energy reserves and nutritional availability from the periphery. The impaired insulin signaling in hypothalamic neurons reduces satiety signals which results in increased food consumption and subsequent weight gain. Insulin resistance decreases energy expenditure through its impact on thermogenesis and its influence on autonomic nervous system functions which together result in positive energy balance [72].

The brain's inability to respond to insulin properly in type 2 diabetes makes hyperglycemia worse because it fails to decrease liver glucose production while also failing to enhance peripheral glucose usage. The central defect works together with peripheral insulin resistance in muscle and adipose tissue to create a worse glycemic control outcome. CNS insulin resistance has been shown to disrupt lipid metabolism by promoting increased lipolysis in adipose tissue while causing fat to accumulate in liver and muscle tissues which are characteristic features of metabolic syndrome [73].

The cluster of conditions known as metabolic syndrome which includes central obesity and insulin resistance and dyslipidemia and hypertension is heavily influenced by CNS insulin resistance. The brain's impaired metabolic and cardiovascular regulatory pathways lead to the development of chronic low-grade inflammation and endothelial dysfunction in metabolic syndrome [74].

CNS insulin resistance functions as both an initiating factor and an outcome of systemic metabolic problems. The disruption of neural control over energy balance together with peripheral insulin action creates pathological feedback loops which maintain and intensify obesity and T2DM and metabolic syndrome. The therapeutic potential of targeting CNS insulin signaling pathways exists to break these cycles and enhance metabolic health [75].

CNS INSULIN RESISTANCE AND NEURODEGENERATIVE DISEASES

The central nervous system (CNS) establishes insulin resistance, serving as a primary pathological cause for neurodegenerative disorders, including Alzheimer's disease (AD). Research shows that impairments in brain insulin signaling contribute to the molecular and cellular abnormalities observed in Alzheimer's disease (AD), prompting some scientists to refer to AD as "Type 3 diabetes" due to its brain-specific insulin resistance pattern, which parallels systemic diabetes [76].

LINK WITH ALZHEIMER'S DISEASE ("TYPE 3 DIABETES")

Alzheimer's disease (AD) leads to gradual memory deterioration and cognitive loss, marked by neuropathological features like amyloid-beta (Aβ) plaques and hyperphosphorylated tau protein that forms neurofibrillary tangles. The brain's insulin system regulates crucial neuronal activities, encompassing energy consumption, synaptic plasticity, and cellular survival mechanisms. The hippocampus and cerebral cortex, along with other brain

areas, possess many insulin receptors that are essential for cognitive functioning [77]. The expression of insulin receptors significantly diminishes, and their signaling efficacy lowers in individuals with Alzheimer's disease. The activation of crucial downstream signaling pathways, such as the phosphoinositide 3-kinase (PI3K)-Akt pathway, is compromised owing to central nervous system (CNS) insulin resistance, which typically safeguards neurons and preserves synapses. The impairment of insulin action inhibits neurons from absorbing and metabolizing glucose, leading to energy deficits that increase their vulnerability to oxidative stress and mitochondrial dysfunction [78].

Term "Type 3 diabetes" describes how brain insulin resistance produces similar metabolic problems to peripheral insulin resistance in systemic diabetes which results in neurodegeneration. Research on AD brains after death demonstrates that these brains show lower insulin receptor sensitivity together with decreased insulin and insulin-like growth factor (IGF) levels and impaired insulin signaling components which support this concept [79].

COGNITIVE IMPAIRMENT AND SYNAPTIC DYSFUNCTION

The brain's insulin resistance disrupts cognitive function through its impact on synaptic plasticity which enables synapses to modify their strength for learning and memory processes. The cellular mechanism of memory formation through long-term potentiation (LTP) receives enhancement from insulin signaling which controls neurotransmitter receptor movement and synaptic protein generation [80].

The failure of insulin signaling triggers synaptic dysfunction to occur. The synapse receives fewer glutamate receptors including AMPA and NMDA receptors which results in weakened excitatory neurotransmission. Insulin resistance causes three main synaptic problems: reduced protein synthesis and impaired spine formation and increased synaptic elimination which together result in diminished synaptic connections. The synaptic changes in AD and related dementias lead to worsening deficits in episodic memory and executive function and other cognitive domains [81].

AMYLOID-BETA AND INSULIN SIGNALING INTERFERENCE

The brains of AD patients contain abnormally accumulated amyloid-beta (Aβ) peptides which stem from amyloid precursor protein (APP) cleavage to form neurotoxic extracellular plaques. The pathological accumulation of Aβ worsens because CNS insulin resistance affects both Aβ metabolism and clearance processes (Figure 10) [82].

The normal function of insulin depends on its ability to enhance the activity of insulin-degrading enzyme (IDE) which breaks down both insulin and Aβ. The reduction of IDE activity occurs when brain insulin signaling becomes impaired which results in decreased Aβ clearance and subsequent plaque formation. The elevated Aβ levels create a harmful feedback loop by damaging insulin receptor function through enhanced receptor internalization and degradation which intensifies insulin resistance [83].

Aβ oligomers disrupt insulin receptor substrate (IRS) phosphorylation by increasing serine phosphorylation which blocks downstream signaling. The vicious cycle between Aβ pathology and impaired insulin signaling accelerates

neurodegenerative processes through their mutual interaction [84].

The lack of insulin's inhibitory influence through Akt results in heightened activation of glycogen synthase kinase 3 beta (GSK3β), leading to tau pathology due to dysregulation. The increased phosphorylation of tau by hyperactive GSK3β leads to the creation of neurofibrillary tangles, which precipitates neuronal death and dysfunction in Alzheimer's disease [85].

MOOD DISORDERS AND CNS INSULIN DYSREGULATION

Research findings demonstrate that CNS insulin dysregulation creates a link with mood disorders particularly depression. Insulin controls neurotransmitter systems which include serotonin dopamine and gamma-aminobutyric acid (GABA) because these substances play essential roles in mood regulation (Figure 11). The disruption of brain insulin signaling pathways leads to problems with neurotransmitter production and release and receptor function which results in mood disturbances [86].

The HPA axis function changes when insulin resistance occurs because this axis regulates stress responses and mood disorders. The neurocircuitry responsible for emotional regulation becomes affected by the inflammatory and oxidative stress conditions that develop from insulin resistance. Research into CNS insulin dysfunction and mood disorders creates new possibilities for developing therapeutic methods that target insulin pathways to enhance mental health treatment [87].

EMERGING THERAPIES TARGETING CENTRAL INSULIN PATHWAYS

The advancement of therapeutic approaches to restore or enhance central insulin sensitivity is ongoing, as central nervous system insulin signaling is crucial in metabolic and neuropsychiatric disorders. The nasal administration of insulin presents a promising approach to directly access the brain while circumventing the blood-brain barrier. Research investigations indicate that intranasal insulin treatment improves cognitive functions in individuals with moderate cognitive impairment and Alzheimer's disease [88].

The reduction of insulin resistance becomes possible through CNS inflammation targeting anti-inflammatory agents which control neuroimmune pathways to protect neuronal function. Research continues to explore the pharmacological adjustment of insulin signaling components together with mitochondrial enhancers and antioxidants [89].

Physical activity and dietary changes continue to serve as essential lifestyle interventions which boost both peripheral and central insulin sensitivity. The combination of pharmacological treatments with lifestyle modifications has shown potential to produce enhanced therapeutic effects [90].

CONCLUSION

CONCLUSION AND FUTURE PERSPECTIVES

The review identifies insulin resistance in the central nervous system as a principal factor contributing to metabolic dysfunction, the progression of neurodegenerative diseases, and neuropsychiatric disorders. The brain uses insulin signaling pathways to regulate energy balance, glucose metabolism, cognitive function, and mood modulation. The disruption of these networks induces many clinical outcomes that culminate in

obesity, type 2 diabetes, Alzheimer's disease, and mental problems.

The identification of CNS insulin resistance creates new possibilities for medical diagnosis and treatment approaches. The clinical use of intranasal insulin and anti-inflammatory treatments shows promise but requires additional extensive clinical trials to confirm their safety and effectiveness. The combination of metabolic and neurological approaches will lead to better management of diseases that affect both systems.

The future of research should concentrate on revealing the exact molecular processes of CNS insulin resistance while developing specific biomarkers for early detection and creating targeted therapeutic approaches. The complete treatment of these conditions requires understanding how peripheral and central insulin resistance interact with each other. A multidisciplinary approach will drive essential progress in patient care and extended treatment outcomes for metabolic and neurodegenerative disorders.

CONFLICT OF INTEREST

There are no conflicts of interest.

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FIGURES

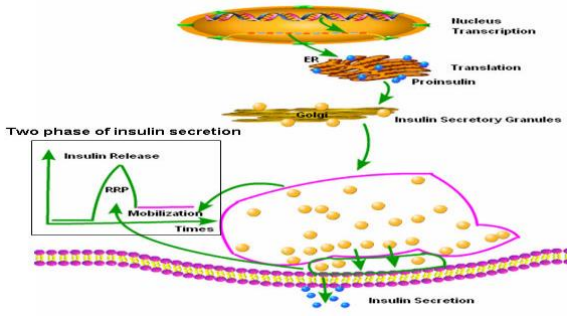

Figure 1. Biosynthesis and Secretion of Insulin in Pancreatic β-Cells

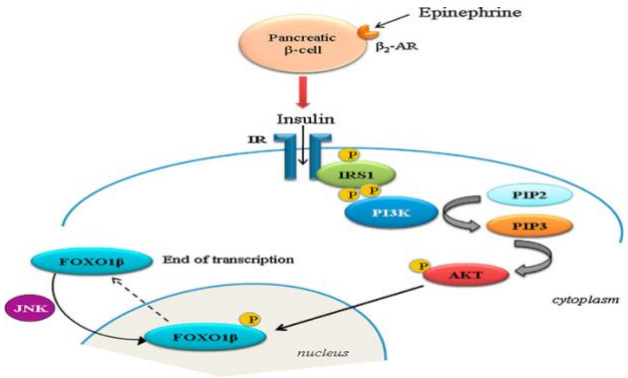

Figure 2. Canonical Insulin Signaling Pathways: PI3K-Akt and MAPK Cascades

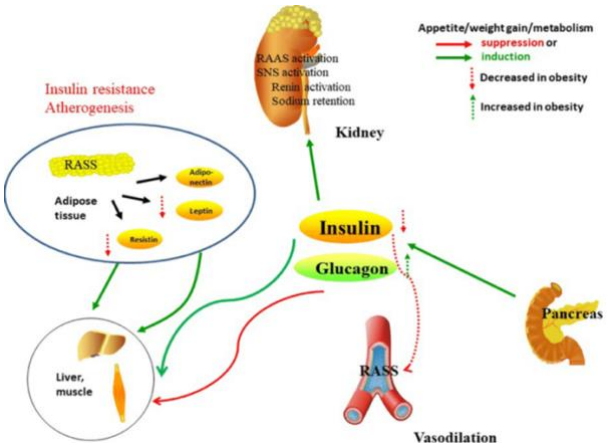

Figure 3. Tissue-Specific Actions of Insulin in Muscle, Liver, and Adipose Tissue

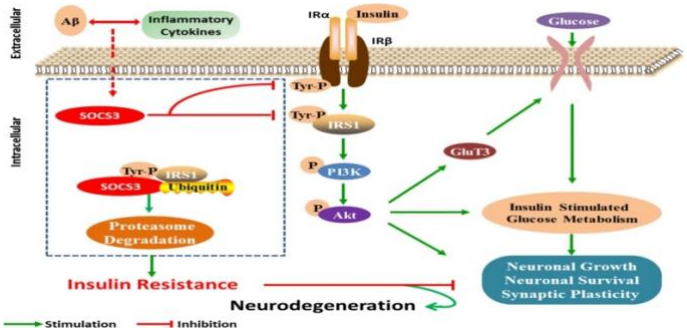

Figure 4. Molecular Disruption of Insulin Signaling via Serine Phosphorylation and SOCS-Mediated IRS Degradation

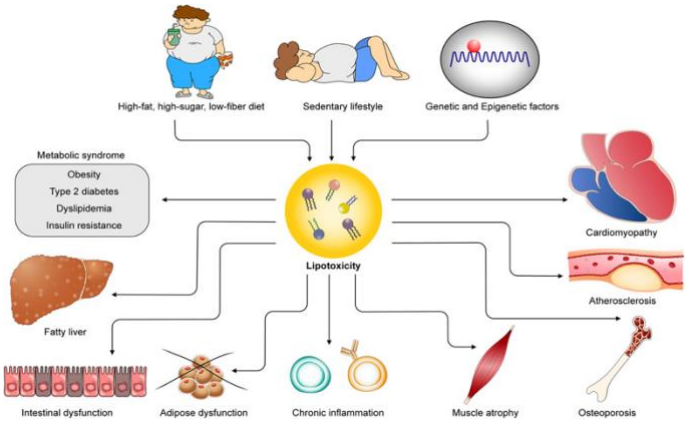

Figure 5. Obesity-Induced Lipotoxicity and Its Impact on Muscle and Liver Insulin Sensitivity.

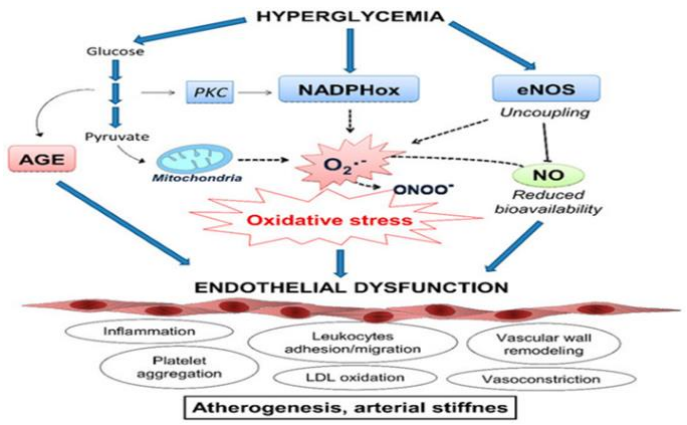

Figure 6. The Role of Inflammation, Oxidative Stress, and ER Stress in Peripheral Insulin Resistance.

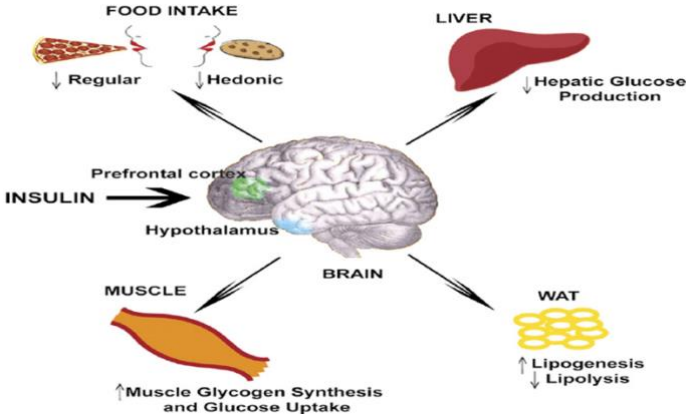

Figure 7. Central Insulin Signaling Pathways in the Hypothalamus and Their Effects on Appetite and Peripheral Glucose Metabolism

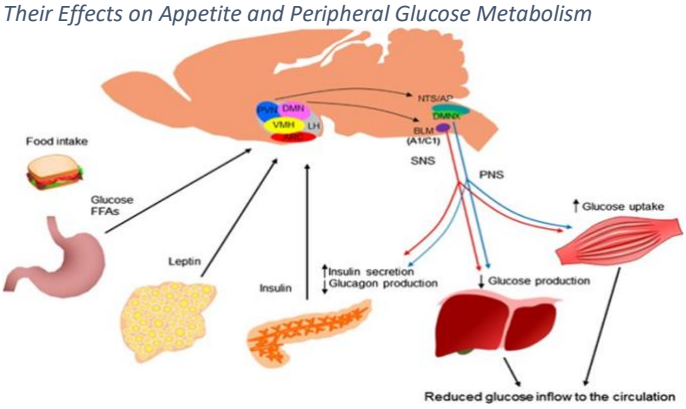

Figure 8. Hypothalamic Control of Food Consumption and Glucose Homeostasis in Relation to Insulin.

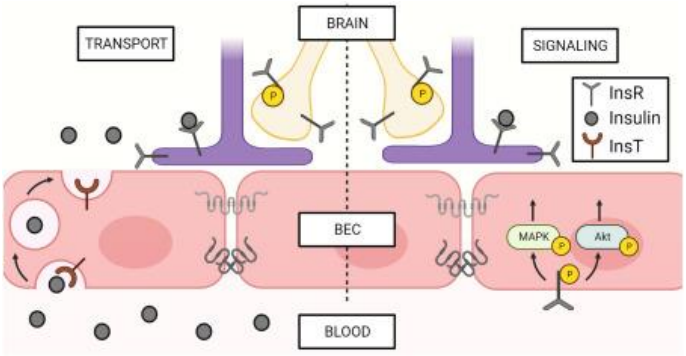

Figure 9. Insulin Transport Across BBB.

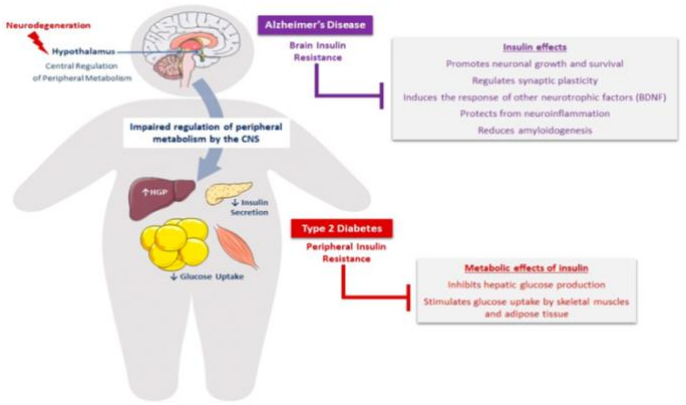

Figure 10. Interplay Between Central Insulin Resistance, Amyloid-Beta Accumulation, and Synaptic Dysfunction in Alzheimer's Disease.

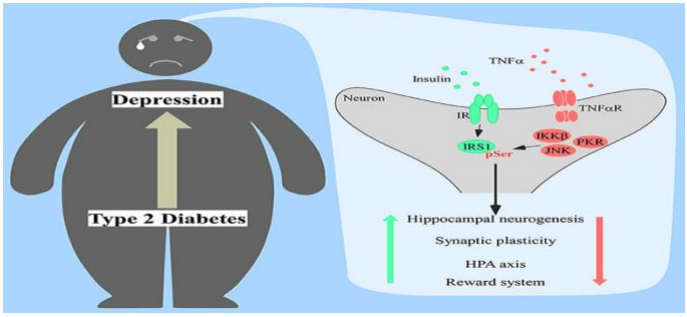

Figure 11 Role of Brain Insulin Signaling in Neurotransmitter Regulation and Mood Disorders.