Content available at: https://www.ipinnovative.com/open-access-journals

IP International Journal of Comprehensive and Advanced Pharmacology

Journal homepage: https://www.ijcap.in/

Review Article

Insulin resistance and neurodegenerative diseases

Akshmita Gairola[1], Anil Kumar Prajapati[1]*, Mustakim Mansuri[1]

[1]*Dept. Pharmacy, L.M. College of Pharmacy, Ahmedabad, Gujarat, India*

ARTICLE INFO

Article history:
Received 08-03-2024
Accepted 16-04-2024
Available online 12-06-2024

Keywords:
Insulin resistance
Neurodegeneration
Alzheimer's disease
Parkinson disease

ABSTRACT

Insulin resistance is a condition where normal or elevated insulin levels fail to elicit the expected biological response, with significant implications for neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD). Despite extensive research, the precise cellular mechanisms driving insulin resistance and its role in neurodegeneration remain elusive. Insights into insulin signaling dysregulation, amyloid-beta accumulation, neuroinflammation, and impaired mitochondrial function shed light on the complex interplay between insulin resistance and neurodegeneration. Various therapeutic strategies targeting insulin resistance, including insulin interventions, GLP-1 analogs, intranasal insulin, and lifestyle interventions, offer promising avenues for mitigating disease progression. This review provides a comprehensive overview of insulin resistance and its association with neurodegenerative disorders, highlighting key molecular and cellular insights, therapeutic approaches, and future directions.

1. Introduction

Insulin resistance refers to a condition where normal or elevated levels of insulin fail to elicit the expected biological response. While much research has focused on understanding insulin-stimulated glucose uptake, the precise cellular mechanisms driving this phenomenon remain elusive.[1] Conversely, insulin resistance has been recognized long before the onset of hyperglycemia and the diagnosis of Type 2 diabetes. Currently, it appears that insulin resistance is closely associated with a combination of risk factors, predisposing individuals to a heightened risk of developing neurodegenerative diseases at an accelerated rate.[2] Neurodegenerative disorders constitute a class of illnesses characterized by the gradual deterioration of the nervous system's structure and function. Primarily driven by the loss of neurons, these conditions can impair various aspects of human functionality, including speech, movement, and cognition. Prominent examples include Parkinson's disease, Alzheimer's disease, and Huntington's disease, which collectively afflict millions worldwide. Environmental and genetic factors intersect to contribute to the onset of these disorders, for which there is currently no known cure. Treatment strategies focus on managing symptoms, alleviating pain, and enhancing mobility. Parkinson's disease, for instance, targets the brain's dopamine-producing neurons, leading to symptoms such as tremors, rigidity, bradykinesia, and postural instability. While existing therapies can alleviate these symptoms to some extent, they do not halt or slow the disease's progression. A recent study has revealed a significant association between insulin resistance and neurodegenerative disorders, including Parkinson's disease (PD) and Alzheimer's disease (AD). Insulin resistance, characterized by reduced responsiveness of cells to insulin, is implicated through various mechanisms:[3,4]

* *Corresponding author.*
E-mail address: prajapatianilkumar1708@gmail.com (A. K. Prajapati).

https://doi.org/10.18231/j.ijcaap.2024.013

A. Brain insulin resistance: Research suggests that individuals with AD exhibit higher rates of peripheral insulin resistance compared to control subjects.[5] Even in the absence of type 2 diabetes, this condition is linked to an increased risk of AD. Insulin resistance in the brain can lead to impairments in immune response, metabolism, and synaptic connections.[4]

B. Role of insulin signaling: Insulin signaling plays a pivotal role in the onset and progression of neurodegenerative diseases.[6] Anomalies associated with insulin signaling and metabolic dysfunction are thought to contribute to the development of AD and PD.

C. Potential therapeutic targets: Targeting insulin signaling and resistance has emerged as a promising therapeutic approach for neurological diseases.[7] Researchers are exploring the neuroprotective effects of medications that enhance insulin sensitivity, such as glucagon-like peptide-1 (GLP-1) receptor agonists, through preclinical and clinical trials.

1.1. Brain insulin signalling and pathways involved in insulin resistance and neurodegenerative diseases

Similar to the insulin receptors found in the periphery and hypothalamus, brain insulin receptors also seem to operate in the hippocampus by initiating the PI3K signaling pathway. Typically, PI3K has been highlighted in literature as the probable signaling pathway for insulin activities in the brain. However, other processes likely play a significant role. For example, in the hypothalamus of insulin-resistant animals, insulin directly influences ATP-gated potassium channels, with reduced capacity to activate these channels, thus affecting neuronal activity modulation. Since altering hippocampal KATP channels has been shown to impact memory function, insulin likely has the ability to regulate hippocampal activity through this pathway independently or in combination.[8]

Insulin binds to a membrane-spanning receptor tyrosine kinase (RTK), which is a glycoprotein embedded in the cellular membrane. This receptor consists of an extracellular domain with two α-subunits and an intracellular catalytic domain with two β-subunits. The α-subunits serve as insulin receptors, while insulin itself acts as a ligand, forming a receptor-ligand complex upon binding. Insulin binding to the α-subunit induces a conformational change in the protein, activating the tyrosine kinase domains on each β-subunit. This tyrosine kinase activity leads to autophosphorylation of multiple tyrosine residues within the β-subunit, with phosphorylation of three specific residues necessary for amplifying the kinase activity. Autophosphorylation then triggers the activation of docking proteins, such as IRS, to which Phosphatidylinositol-3-Kinase (PI-3K) or GRB2, where the ras Guanine nucleotide exchange factor (GEF), also known as SOS, can attach. PI-3K phosphorylates PIP2 to PIP3, serving as a docking site for PDPK1 and Protein kinase B (AKT), which in turn phosphorylates AKT and PK2, activating them. This cascade of events plays crucial roles in metabolic functions, including lipid, protein, and glycogen synthesis, as well as cell survival and proliferation. Particularly significant is the involvement of the PI-3K pathway in glucose distribution for essential cellular functions, such as suppressing hepatic glucose synthesis and activating glycogen synthesis. AKT plays a pivotal role in linking the glucose transporter (GLUT4) to the insulin signaling pathway. Activated GLUT4 translocates to the cell membrane, facilitating glucose transportation into the intracellular medium. The insulin transduction pathway is a biochemical cascade through which insulin enhances glucose uptake into fat and muscle cells while reducing glucose synthesis in the liver, thus contributing to maintaining glucose homeostasis. This pathway is subject to modulation by various factors, including fed versus fasting states, stress levels, and other hormones.[8]

1.2. Impaired Insulin signalling Pathways in Alzheimer's and Parkinson's Diseases

Preclinical investigations have uncovered altered insulin signaling pathways and downstream effects in animal models of Alzheimer's disease (AD) and Parkinson's disease (PD), contributing to disease progression. Recent discoveries have revealed desensitized insulin signaling in the brains of AD and PD patients, marked by inactivation of insulin and insulin-like growth factor 1 (IGF-1) receptors, as well as insulin receptor substrates 1 and 2 (IRS1/2), and key second messenger kinases such as Akt and mTOR. These observations parallel findings in peripheral diabetes, leading some researchers to characterize AD as "type 3 diabetes". However, unlike diabetes where elevated insulin and glucose levels drive desensitization, insulin desensitization in AD and PD patients, even in non-diabetics, is likely triggered by chronic brain inflammation. Pro-inflammatory cytokines, such as tumor necrosis factor (TNF), block growth factor signaling, further exacerbating insulin resistance. Given the essential role of insulin in neuronal development and maintenance, desensitization increases the risk of neuronal damage over time, contributing to neurodegeneration. Evidence from cerebrospinal fluid (CSF) analyses in early disease stages, showing decreased levels of insulin, IGF-1, nerve growth factor, and glial-derived neurotrophic factor alongside increased neuroinflammatory markers, underscores the significance of brain insulin resistance in AD pathogenesis. Pathophysiological mechanisms underlying brain insulin/IGF resistance in AD include progressive loss of insulin/IGF-responsive neurons due to trophic factor withdrawal and impaired ligand-receptor binding resulting from pathological changes in membrane lipid composition, likely leading to reduced receptor

expression. The concept of AD as a brain-specific or brain-restricted form of diabetes mellitus, termed "Type 3 Diabetes," stems from the recognition of both insulin/IGF insufficiency and resistance primarily within the central nervous system (CNS).[9] Mitochondrial dysfunction, which extends to neurons, is intricately linked to both diabetes and cellular insulin resistance (IR). Research indicates that neural cells displaying insulin resistance experience compromised mitochondrial biogenesis, depolarization of mitochondrial membrane potential, and increased levels of reactive oxygen species (ROS). Additionally, in diabetic rats, elevated levels of SNCA (Alpha-synuclein protein) have been observed in Purkinje cells.[10]

2. Molecular and Cellular Insights in Neurodegeneration Caused by Insulin Resistance

Neurodegeneration linked to insulin resistance involves intricate biochemical pathways with various components. These mechanisms include:

1. Insulin signaling dysregulation: Insulin resistance, characterized by reduced insulin sensitivity, can lead to compromised brain glucose metabolism in Alzheimer's disease (AD), potentially contributing to neurodegeneration.[11] Additionally, insulin resistance in the brain can heighten oxidative stress, a known factor in the development and advancement of neurodegenerative disorders.[3]
2. Amyloid-beta accumulation and Tau phosphorylation: Insulin resistance in the brain is associated with increased deposition of amyloid-beta and elevated tau phosphorylation, both implicated in AD onset.[12]
3. Neuro-inflammation: Neurodegenerative diseases, including AD, often exhibit neuroinflammatory features. Insulin resistance may play a role in initiating neuroinflammatory conditions, exacerbating neurodegeneration.
4. Impaired mitochondrial function: Reduced mitochondrial function resulting from brain insulin resistance can contribute to neurodegeneration.

AD as "type 3 diabetes": Due to the brain's insulin resistance, AD has been coined "type 3 diabetes," potentially influencing the disease's onset and progression.[13] Understanding the molecular mechanisms underlying insulin resistance-induced neurodegeneration is crucial for developing innovative therapeutic strategies to decelerate the progression of neurodegenerative diseases like AD.[14]

2.1. Therapeutic approaches in neurodegeneration due to insulin remittance

Various therapeutic strategies targeting insulin resistance aim to mitigate the progression of neurodegenerative diseases. These include:

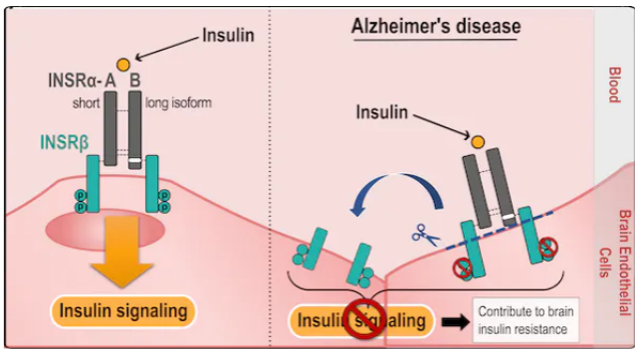

Figure 1: Insulin signalling in Alzheimer's disease

1. Insulin interventions: Studies have shown that insulin treatment in Alzheimer's disease (AD) can improve hypometabolism, spatial memory, inflammation, and reduce amyloidogenic buildup and Tau hyper phosphorylation, indicating a potential for addressing brain insulin resistance in AD patients.[11,13]
2. GLP-1 analogs: Preclinical research suggests that GLP-1 receptor agonists can overcome brain insulin resistance in AD. Clinical trials have demonstrated improvements in inflammation markers, neuronal energy consumption, and pathological brain activity in AD/MCI patients treated with GLP-1 analogs.[7]
3. Intranasal insulin: Intranasal insulin treatment has demonstrated neuroprotective effects in AD by directly delivering insulin to the brain, bypassing the blood-brain barrier and potentially reducing neurodegeneration.[7]
4. Combination therapies: Combining treatments for neurodegenerative diseases with anti-tau or anti-amyloid therapies may enhance efficacy.[3]
5. Prevention and lifestyle interventions: Lifestyle changes such as a balanced diet, regular exercise, and weight control can help prevent insulin resistance and potentially slow the progression of neurodegenerative diseases.[4]

Further research is needed to establish the effectiveness and safety of these therapeutic approaches in broader patient populations, despite promising results from preclinical and some clinical trials. Investigating alternative therapeutic targets and strategies is crucial for developing more potent treatments for neurodegenerative diseases like Parkinson's and Alzheimer's.[15,16]

2.2. Future direction

1. Precision medicine approaches: Tailoring treatment strategies based on individual patient profiles, including genetic, metabolic, and lifestyle factors,

could optimize therapeutic outcomes and minimize adverse effects.

2. Targeting novel pathways: Exploring alternative therapeutic targets beyond traditional insulin signaling pathways may uncover new avenues for intervention. This could involve investigating molecular mechanisms underlying insulin resistance-induced neurodegeneration and identifying potential druggable targets.
3. Combination therapies: Developing synergistic treatment regimens that combine interventions targeting insulin resistance with other disease-modifying therapies, such as anti-amyloid or anti-tau agents, may lead to more effective disease management and slower disease progression.
4. Biomarker discovery: Identifying reliable biomarkers for early detection and monitoring of neurodegenerative diseases and insulin resistance could facilitate timely intervention and personalized treatment approaches.
5. Lifestyle interventions: Further research into the effects of lifestyle factors, such as diet, exercise, and stress management, on insulin resistance and neurodegeneration could inform preventive strategies and lifestyle interventions for at-risk individuals.
6. Translational research: Bridging the gap between preclinical findings and clinical applications through translational research efforts will be crucial for translating promising therapeutic approaches into effective treatments for patients with neurodegenerative diseases.

3. Conclusion

In conclusion, insulin resistance plays a crucial role in neurodegenerative diseases like Alzheimer's and Parkinson's. Understanding its molecular mechanisms opens avenues for therapeutic interventions. While promising treatments exist, further research is needed to ensure their effectiveness and safety. Future directions, including precision medicine and lifestyle interventions, offer hope for improved patient outcomes. Collaborative efforts are key to advancing our understanding and developing effective strategies against these debilitating diseases.

4. Source of Funding

None.

5. Conflict of Interest

None.

References

1. Cefalu WT. Insulin resistance: cellular and clinical concepts. *Exp Biol Med (Maywood)*. 2001;226(1):13–26.
2. Petersen MC, Shulman GI. Mechanisms of Insulin Action and Insulin Resistance. *Physiol Rev*. 2018;98(4):2133–223.
3. De La M. Insulin Resistance and Neurodegeneration: Progress Towards the Development of New Therapeutics for Alzheimer's Disease. *Drugs*. 2017;77(1):47–65.
4. Arnold SE, Arvanitakis Z, Macauley-Rambach SL, Koenig AM, Wang HY, Ahima RS, et al. Brain insulin resistance in type 2 diabetes and Alzheimer disease: concepts and conundrums. *Na Rev Neurol*. 2018;14(3):168–81.
5. Femminella GD, Livingston NR, Raza S, Doef TD, Frangou E, Love S, et al. Does insulin resistance influence neurodegeneration in non-diabetic Alzheimer's subjects? *Alzheimers Res Ther*. 2021;13(1):47.
6. Takamatsu Y, Ho G, Koike W, Sugama S, Takenouchi T, Waragai M. Combined immunotherapy with "anti-insulin resistance" therapy as a novel therapeutic strategy against neurodegenerative diseases. *NPJ Parkinsons Dis*. 2017;p. 1–4.
7. Hölscher C. Brain insulin resistance: role in neurodegenerative disease and potential for targeting. *Expert Opin Invest Drugs*. 2020;4:333–48.
8. Mcnay EC, Recknagel AK. Brain insulin signaling: a key component of cognitive processes and a potential basis for cognitive impairment in type 2 diabetes. *Neurobiol Learn Mem*. 2011;96(3):432–42.
9. De La M. Insulin resistance and Alzheimer's disease. *BMB Rep*. 2009;42(8):475–81.
10. Hong CT, Chen KY, Wang W, Chiu JY, Wu D, Chao TY, et al. Insulin Resistance Promotes Parkinson's Disease through Aberrant Expression of α-Synuclein, Mitochondrial Dysfunction, and Deregulation of the Polo-Like Kinase 2 Signaling. *Cells*. 2020;9(3):740.
11. Berlanga-Acosta J, Nieto GG, Rodríguez NR, Bringas-Vega ML, Del-Barco-Herrera G, Berlanga-Saez D. Insulin Resistance at the Crossroad of Alzheimer Disease Pathology: A Review. *Front Endocrinol*. 2020;p. 560375.
12. Ferreira L, Fernandes CS, Vieira M, Felice D. Insulin Resistance in Alzheimer's Disease. *Front Neurosci*. 2018;p. 1–12.
13. Talbot K. Brain insulin resistance in Alzheimer's disease and its potential treatment with GLP-1 analogs. *Neurodegener Dis Manag*. 2014;4(1):31–40.
14. Sędzikowska A, Szablewski L. Insulin and Insulin Resistance in Alzheimer's Disease. *Int J Mol Sci*. 2021;22(18):9987. doi:10.3390/ijms22189987.
15. Dierssen M. Frontiers _ Editorial_ Brain Insulin Resistance in Neurodevelopmental and Neurodegenerative Disorders_ Mind the Gap!". *Front Neurosci*. 2021;15:730378.
16. Kellar D, Craft S. Brain insulin resistance in Alzheimer's disease and related disorders: mechanisms and therapeutic approaches. *Lancet Neurol*. 2020;19(9):758–66.

Author biography

Akshmita Gairola, Student

Anil Kumar Prajapati, Research Scholar https://orcid.org/0000-0001-6068-0616

Mustakim Mansuri, Associate Professor https://orcid.org/0000-0002-8591-1908

Cite this article: Gairola A, Prajapati AK, Mansuri M. Insulin resistance and neurodegenerative diseases. *IP Int J Comprehensive Adv Pharmacol* 2024;9(2):87-90.