Review

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Neuropharmacological Insights into Type 3 Diabetes: Molecular Mechanisms, Therapeutic Advances, and Future Directions

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Diabetes mellitus is a multifaceted metabolic disease with consequences for global health. It is characterized by insulin resistance and irregularities in insulin secretion. The global prevalence of diabetes necessitates a nuanced understanding beyond traditional classifications, emphasizing the dynamic nature of this health threat. Recent strides in genetics have led to the development of personalized treatments, while the emergence of type 3 diabetes underscores the need for refined classifications, standardized definitions, and improved screening methods. The fusion of neuropharmacology with diabetes care signals a transformative shift, with a focus on cognitive function and neuronal survival alongside glycaemic control. Repurposing antidiabetic medications for neurodegenerative diseases introduces a promising frontier at the intersection of diabetes and neurological research. Investigating the molecular and metabolic pathways that underlie diabetic problems reveals complex processes, including the generation of diacylglycerol, modified redox states, the polyol pathway, and advanced glycation end-product synthesis. Strategies targeting these pathways unveil novel therapeutic strategies to mitigate vascular dysfunction and oxidative stress. Antidiabetic drugs, including metformin, thiazolidinediones, and glucagon-like peptide-1 receptor-targeting compounds, show promise for neuroprotection, extending beyond glycaemic control to enhance insulin signaling and protect against degeneration. Molecular targets such as peroxisome proliferator-activated receptors (PPARs), protein tyrosine phosphatase 1B (PTP-1B), and glycogen synthase kinase-3 (GSK-3) offer potential avenues for reshaping diabetes management, presenting both challenges and opportunities in the pursuit of precision medicine. In envisioning the future, the concept of type 3 diabetes will become a focal point, leading to dedicated exploration for accurate diagnostics and targeted treatments. This paper serves as a catalyst for sustained exploration, interdisciplinary collaboration, and an unwavering commitment to pioneering the future of diabetes care, aiming to illuminate the present while shaping a future met with precision, empathy, and innovative solutions.

Keywords: type 3 diabetes; neurodegenerative diseases; insulin resistance; molecular mechanisms; antidiabetic drugs

Introduction

Diabetes mellitus is a complex metabolic disease with numerous characteristics, which is becoming more obvious [1]. Diabetes is characterized by insulin resistance and insulin secretion irregularities, which can lead to a range of complications, including diabetic kidney disease [2]. With type 1 and type 2 diabetes being the most common types of diabetes, this illness poses a serious threat to world health [3]. Recent discoveries have linked diabetes and its consequences to genetics, potentially opening the door to tailored treatments [4]. Recent studies have shed light on the complex relationships between diabetes, neurodegeneration, and biological processes, broadening our understanding of this disease. With the introduction of the idea of "type 3" diabetes [5], which connects dementia, especially Alzheimer's disease (AD), to insulin resistance in the brain, new avenues have been opened for research. The term type 3 diabetes has been proposed to describe a condition where insulin resistance manifests specifically within

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the brain, distinct from classical type 1 and type 2 diabetes affecting peripheral tissues. More evidence was provided in favour of this theory by the emphasis on the role that hyperglycaemia plays in initiating neurodegenerative processes [6]. The complex nature of diabetes has been highlighted in different ways by several researchers, with one study investigating the effects of hyperglycemia on neurodegeneration [7], specifically in Alzheimer's disease, and another outlining several pathways involved in the pathogenesis of this disease [8]. Together, these investigations highlight the need for additional investigations into the intricate interactions among diabetes, neurodegeneration, and cellular pathways as well as the necessity for therapeutic approaches. The necessity for comprehensive knowledge of the numerous manifestations of diabetes is highlighted by the global prevalence of this disease [9]. Although fundamental, traditional classifications have drawbacks, and the advent of subgroups such as type 3 emphasizes how diabetes science is always changing [10]. One of the biggest obstacles to creating a comprehensive worldwide picture of diabetes has been the absence of standardization in the definition and classification of the condition [11] for the patient community mostly concentrated in developing countries. Better screening and management techniques are needed due to the increasing number of diabetic patients [12]. Unravelling the molecular intricacies of diabetes is essential for comprehending its underlying pathophysiology. Exploring the cellular mechanisms underlying the progression from pancreatic malfunctions to enigmatic type 3 diabetes is critical for understanding the complexities associated with microvascular and macrovascular complications.

The field of neuropharmacology and antidiabetic medications is currently changing, with an emphasis on improving cognitive function and neuronal survival in addition to glycemic management [13,14]. This approach is especially pertinent in light of type 3 diabetes, which emphasizes the necessity of managing this condition holistically and using neuropharmacology [15,16]. Additional research is being conducted on the possibility of using antidiabetic medications, including metformin, thiazolidinediones, and those that target the glucagon-like peptide-1 receptor to improve memory and cognition by supporting neuronal survival [15]. Moreover, an interesting field of study is the repurposing of these medications in conjunction with insulin for the prevention and therapy of neurodegenerative ailments such as Parkinson's disease (PD) and AD [16]. Precision interventions take centre stage, exploring molecular targets such as peroxisome proliferator-activated receptors (PPARs), protein tyrosine phosphatase 1B (PTP-1B), and glycogen synthase kinase-3 (GSK-3) inhibitors. These targeted approaches open avenues for personalized therapeutic strategies, heralding a new era of precision medicine in diabetes care.

Cognitive function is significantly influenced by type 3 diabetes, a term increasingly used to characterise insulin resistance unique to the brain [17]. Studies have revealed the complex relationship between compromised brain insulin signaling and the deterioration of cognitive function [17]. Insulin has important impacts on the brain that go beyond its involvement in metabolism. These effects are vital for learning, memory, and other cognitive processes. Type 3 diabetes is characterised by abnormalities in insulin-mediated pathways, which have a role in cognitive function deficits and are thus a significant factor in the development of neurodegenerative diseases [18]. The impact of type 3 diabetes extends to neuronal survival, as insulin resistance jeopardizes the well-being of neurons. Preclinical and clinical studies have shed light on the consequences of compromised insulin signaling pathways [19]. This impairment contributes to neurodegeneration, synaptic dysfunction, and increased vulnerability to conditions like Alzheimer's disease. Understanding the intricate relationship between type 3 diabetes and neuronal survival is crucial for delineating therapeutic strategies that may impede or alleviate the progression of neurodegenerative disorders. Nevertheless, brain insulin resistance, a characteristic feature of type 3 diabetes, refers to the reduced sensitivity of neurons to the signaling of insulin [20]. This event disturbs the intricate equilibrium required for neural homeostasis. The molecular mechanisms that cause brain insulin resistance involve a decrease in the activation of insulin receptors and the subsequent signaling pathways. The disruption of these channels leads to impaired communication between neurons and harm to nerve cells. Understanding the intricate nature of brain insulin resistance in type 3 diabetes is crucial for developing specific therapies that target the underlying factors contributing to cognitive decline and neurodegeneration. Future work involves exploring research horizons where personalized therapeutics and collaborative efforts converge. The concept of type 3 diabetes has become a focal point, necessitating dedicated exploration for accurate diagnostics and targeted treatments. In charting a course for transformative breakthroughs, this paper serves as a catalyst for sustained exploration, interdisciplinary collaboration, and an unwavering commitment to pioneering the future of diabetes care.

Pathophysiological Foundations of Patients with Type 3 Diabetes

The connection between neurodegeneration and diabetes is known as type 3 diabetes, and it is a complicated illness with many underlying causes. The importance of insulin resistance and insufficiency in the aetiology of neurodegenerative illnesses, including Alzheimer's disease, has been highlighted in different research paradigms [7,21]. Type 3 diabetes, also known as brain diabetes, is a complex condition that links diabetes and neurodegeneration. It is characterized by insulin resistance and deficiency in the brain, abnormal glucose metabolism, and

molecular and biochemical abnormalities that contribute to the development of neurodegenerative diseases, particularly Alzheimer's disease. The pathophysiological foundations of type 3 diabetes are not fully understood, but recent research has shed light on the mechanisms underlying insulin resistance [5,22] and deficiency in the brain, abnormal glucose metabolism and energy deficits, and molecular and biochemical abnormalities in neurodegeneration. Insulin resistance mediates the dysregulation of bioenergetics and progression to Alzheimer's disease [23]. A biological mechanism linking diabetes to changes in brain structure and function that could contribute to the development of depression might also exist [24].

A better understanding of the pathophysiological foundations of type 3 diabetes is crucial for the development of effective therapeutic strategies to prevent or treat neurodegenerative diseases. Insulin is an important hormone that regulates glucose metabolism and energy production in the brain. Insulin resistance hinders the body's capacity to effectively use glucose as an energy source, resulting in cellular energy deficiencies [25]. Due to cellular resistance to insulin's signals for glucose uptake, glucose accumulates in the bloodstream, leading to a deprivation of cells' principal energy source. This metabolic inefficiency initiates compensatory mechanisms, which stimulate the degradation of lipids, leading to heightened oxidative stress. Increased levels of oxidative stress are a contributing factor to cellular damage, inflammation, and decreased function, creating a harmful environment associated with numerous health difficulties, such as cardiovascular illnesses and neurological disorders [26]. Studies have shown that insulin resistance and its deficiency are associated with the development of AD. In fact, some researchers have proposed that AD represents a brain-specific form of diabetes mellitus, also known as type 3 diabetes. This is due to the fact that AD is frequently linked, even despite the absence of type 2 diabetes, obesity, or peripheral insulin resistance, to growing brain insulin resistance. The molecular, metabolic, and signal transduction problems found in AD patients are essentially the same as those found in people with type 1 and type 2 diabetes mellitus, according to postmortem investigations. Insulin resistance and deficiency in the brain are thought to be caused by a combination of genetic and environmental factors. The genetic factors that contribute to insulin resistance and deficiency include mutations in genes that regulate insulin signaling pathways, glucose metabolism, and energy production. Environmental factors that contribute to insulin resistance and deficiency include a high-fat diet, sedentary lifestyle, and exposure to toxins and pollutants.

Abnormal glucose metabolism and energy deficits are key features of type 3 diabetes and are closely linked to the pathogenesis of neurodegenerative diseases, particularly Alzheimer's disease (AD) [27,28]. The brain relies heavily on glucose as a primary energy source, and any disruption in glucose utilization can have profound effects on neuronal function and survival. In the context of type 3 diabetes, impaired glucose uptake and utilization in the brain lead to energy deficits, which in turn contribute to neuronal dysfunction and degeneration [29,30]. This disruption in energy metabolism is often accompanied by increased reactive oxygen species (ROS) production, oxidative stress, mitochondrial dysfunction and DNA damage [31,32]. These molecular and biochemical abnormalities drive proapoptotic, proinflammatory, and pro-amyloid-β protein precursor-amyloid-β (pro-AβPP-Aβ) cascades, all of which are characteristic of neurodegenerative diseases [31]. Moreover, brain glucose utilisation, insulin signaling responses, and insulin-responsive gene expression all decrease with the progression of AD. This decline in glucose utilization and energy deficits contribute to the starvation of brain cells, leading to impairments in homeostasis and increased cell death [31,33]. The link between abnormal glucose metabolism, energy deficits, and neurodegeneration underscores the importance of understanding the mechanisms underlying these processes. The findings also highlight the potential for therapeutic interventions aimed at restoring normal glucose metabolism and energy balance in the brain to mitigate the progression of neurodegenerative diseases associated with type 3 diabetes.

Molecular and biochemical abnormalities are fundamental components of neurodegenerative disorders like AD, and are closely intertwined with the concept of type 3 diabetes [21]. These abnormalities encompass a wide range of cellular and molecular dysfunctions that contribute to the progressive degeneration of neurons and cognitive decline. In the context of type 3 diabetes, the molecular and biochemical abnormalities observed in neurodegenerative diseases are often linked to insulin resistance and deficiency in the brain [31,34]. These include impaired insulin and insulin-like growth factor (IGF) signaling mechanisms, reduced expression of insulin receptor substrate (*IRS*) mRNA, dysregulation of *tau* mRNA, altered activity of kinases involved in tau phosphorylation, and increased amyloid precursor protein (APP) expression [31,34]. These abnormalities are associated with disruptions in neuronal survival, energy production, gene expression, and synaptic plasticity, ultimately leading to neurodegeneration. Furthermore, the accumulation of amyloid-β (Aβ) plaques and neurofibrillary tangles [21] and oxidative stress are hallmark features of AD and other neurodegenerative diseases. These molecular and biochemical abnormalities are thought to arise from dysregulated insulin and IGF signaling [34], impaired glucose utilization, and energy deficits in the brain, all of which are characteristic of type 3 diabetes. Understanding the molecular and biochemical underpinnings of neurodegeneration in the context of type 3 diabetes is crucial for the development of targeted therapeutic strategies aimed at mitigating these abnormalities and preserving neuronal function. By addressing the molecular and biochemical dysfunctions associated with type 3 diabetes, researchers and

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clinicians may uncover new avenues for intervention and treatment in the realm of neurodegenerative diseases.

Insulin resistance and deficiency in the brain are influenced by a complex interplay of genetic and environmental factors, including dysregulation of insulin signaling pathways, glucose metabolism, and energy production [35]. These abnormalities are often accompanied by peripheral insulin resistance, obesity, and metabolic syndrome, all of which contribute to the development of type 2 diabetes mellitus [36]. Brain insulin resistance is a key feature of both type 2 diabetes and Alzheimer's disease, suggesting a potential link between these conditions [37]. The link between type 3 diabetes and neurodegenerative diseases underscores the importance of understanding the neuroendocrine axis and its role in the pathogenesis of these disorders. Dysregulation of the neuroendocrine axis can lead to disruptions in glucose metabolism, energy deficits, and molecular and biochemical abnormalities that contribute to neurodegeneration. Furthermore, the neuroendocrine axis is a potential target for therapeutic interventions aimed at mitigating the progression of neurodegenerative diseases associated with type 3 diabetes. By targeting the neuroendocrine axis, researchers and clinicians may be able to develop new treatments that address the underlying molecular and biochemical abnormalities associated with type 3 diabetes and neurodegeneration.

Our knowledge of the pathophysiology of neurodegenerative illnesses, especially AD, has advanced significantly with the recognition of type 3 diabetes as a sort of neuroendocrine dysfunction. The paradigm shift recognizes the intricate interplay between insulin resistance, abnormal glucose metabolism, and molecular and biochemical abnormalities in the brain, all of which contribute to the development and progression of neurodegeneration. The evidence supporting type 3 diabetes as a neuroendocrine disorder underscores the importance of addressing both central and peripheral aspects of insulin signaling and glucose metabolism in the context of neurodegenerative diseases. By recognizing the brain-specific nature of this form of diabetes, researchers and clinicians can develop targeted therapeutic strategies aimed at preserving neuronal function and mitigating the progression of neurodegenerative diseases. Furthermore, the identification of type 3 diabetes as a neuroendocrine disorder opens new avenues for research into the underlying mechanisms of insulin resistance and deficiency in the brain, as well as the development of novel treatment approaches that target the neuroendocrine axis.

Cellular and Molecular Mechanisms of Diabetic Complications

An autoimmune response causes type 1 diabetes when the immune system mistakenly attacks and destroys the beta cells in the pancreas that produce insulin [38]. This results in an insufficiency of insulin, a crucial hormone for the regulation of glucose [39]. People diagnosed with type 1 diabetes necessitate continuous insulin treatment throughout their lives to regulate their blood glucose levels. Without treatment, it can result in significant problems such as renal damage, cardiovascular disorders, and neurological difficulties. The condition known as insulin resistance is linked to type 2 diabetes, wherein cells do not react to insulin as well as they should. In order to compensate for this, the pancreas may not generate enough insulin [40]. This form of condition is frequently associated with lifestyle variables such as unhealthy eating habits and a lack of physical activity. Left unregulated, it can lead to consequences such as cardiovascular disease, renal impairment, neuropathy, and ocular issues. Common strategies for managing type 2 diabetes and reducing related health risks include making changes to one's lifestyle, taking medication, and undergoing insulin therapy.

Understanding the intricate cellular and molecular mechanisms underlying diabetic complications is important. The complex connection between high blood sugar levels (hyperglycemia) and the damage to small blood vessels in diabetes involves a series of intricate biochemical processes that have a substantial effect on the health of the blood vessels. Diabetes causes hyperglycemia, which triggers the polyol pathway flow. This process converts excess glucose into sorbitol, resulting in osmotic stress and malfunction in cells. The polyol pathway is a crucial player in hyperglycemia-induced damage. It is important to elucidate how increased polyol pathway flux contributes to vascular dysfunction and diabetic microvascular complications. Understanding the biochemical intricacies and downstream effects of this pathway, shedding light on its role in the pathophysiology of diabetes. The polyol pathway, particularly the enzyme aldose reductase, plays a significant role in the development of diabetic complications. Simultaneously, a modified cellular redox state occurs, disturbing the intricate equilibrium between oxidants and antioxidants. The occurrence of oxidative stress triggers many signaling pathways, which worsen the microvascular problems. In addition, elevated blood sugar levels stimulate the production of diacylglycerol (DAG), which in turn activates protein kinase C (PKC), leading to impaired blood vessel function. This PKC facilitates the impact of high blood sugar levels on endothelial cells, leading to the promotion of inflammation, oxidative stress, and changes in the permeability of blood vessels. Another important factor in this situation is the formation of advanced glycation end products (AGEs). Hyperglycemia stimulates the process of non-enzymatic glycation of proteins, resulting in the formation of AGEs that attach to receptors and trigger oxidative stress and inflammation. It contributes to the generation of advanced glycation end products (AGEs) and activates the receptor for AGEs (RAGE), leading to vascular and cellular dysfunction [41].

This pathway also contributes to oxidative stress, a key factor in diabetic complications, by depleting the antioxidant glutathione and increasing the production of malondialdehyde [42]. Furthermore, the activation of poly (ADP-ribose) polymerase-1 (PARP) by hyperglycemia-induced oxidative stress can lead to endothelial dysfunction, a common feature in diabetic complications [43]. The potential of aldose reductase inhibitors for preventing these complications has been demonstrated [44]. The polyol pathway, imbalanced redox state, activation of DAG-PKC, and production of AGEs synergistically alter the equilibrium of microvascular function, resulting in impaired endothelial function, heightened vascular permeability, and inflammation. This dysregulation is a contributing factor to the development of diabetic microvascular problems, such as retinopathy, nephropathy, and neuropathy.

Exploring the effects of an altered cellular redox state in diabetes and explaining how oxidative stress becomes a defining feature of difficulties associated with this disease are important. Additionally, by examining the dysregulation of the cellular redox balance, we connected hyperglycemia and increased production of reactive oxygen species, linking this phenomenon to the progression of complications. Hyperglycaemia-induced vascular dysfunction is a key feature of diabetic complications, in which diacylglycerol (DAG) formation and subsequent activation of protein kinase C (PKC) isoforms play pivotal roles [45–48]. Specifically, the beta- and delta-isoforms of PKC are preferentially activated in the vasculature of diabetic animals, leading to increased production of extracellular matrix and cytokines; enhanced contractility, permeability, and vascular cell proliferation; and inhibition of Na^+-K^+-ATPase [45]. These effects are mediated through the regulation of enzymatic activities and gene expression and can be prevented by PKC inhibitors [47,48]. Vascular permeability increases, extracellular matrix expansion, aberrant angiogenesis, excessive apoptosis, changes in enzymatic activity, and thickening of the basement membrane are all linked to the activation of PKC isoforms, especially the beta1/2 isoform [48]. These findings suggest that targeting the DAG-PKC pathway may be a promising approach for the treatment of diabetic vascular complications.

Diabetes accelerates the production and build-up of advanced glycation end products (AGEs), which might result in vascular problems [49,50]. The interaction of AGEs with the receptor for AGEs (RAGE) results in oxidative stress, which causes vascular inflammation and thrombosis. AGEs also contribute to inflammation, oxidative stress, and atherosclerosis [49–51]. AGEs also play a role in the activation of the redox-sensitive transcription factor NF-κB, which is associated with the development of late diabetic complications [52]. By shifting our focus to diabetic macrovascular disease, we explored the potential role of insulin resistance in its development. Hyperglycaemia, oxidative stress, and inflammatory pathways are implicated in diabetic macroangiopathy, a form of accelerated atherosclerosis [53]. Insulin resistance and hyperglycemia both contribute to the development of atherosclerosis, with a focus on reversing disturbances in glucose and lipid homeostasis [54]. The potential role of macrophage glucose metabolism in diabetic vascular disease has also been highlighted, suggesting a link between glucose metabolism and proinflammatory responses in myeloid cells [55].

Emerging Therapeutic Strategies: Antidiabetic Drugs and Neuropharmacology

Recent research has highlighted the potential of antidiabetic drugs, particularly metformin, thiazolidinediones, and compounds targeting the glucagon-like peptide-1 receptor, to promote neuronal survival and improve memory and cognition [15]. These drugs, which include Glucagon-like peptide-1 (GLP-1) analogs, have been shown to enhance insulin signaling and have neuroprotective effects, making them promising candidates for the treatment of neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease [56–58]. Preclinical studies have shown that these compounds protect against degenerative processes, reduce plaque formation, and improve synaptic and neuronal functionality. Clinical trials are currently underway to further explore the potential of these compounds in treating these brain disorders. The potential of GLP-1R agonists in modifying brain metabolism, neuroinflammation, and regeneration has been demonstrated, with implications for both diabetic and nondiabetic patients [59,60]. These compounds, including exenatide, liraglutide, and semaglutide, have shown promise in treating type 2 diabetes and have been associated with neuroprotective effects, particularly in diabetes-related neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease [61,62]. The development of these compounds has led to significant advancements in the field of medicinal chemistry, with potential applications in the diagnosis of diabetes and pancreatic cancer [62].

Recent research has proposed a link between diabetes and Alzheimer's disease, suggesting a brain insulin-resistant state as a potential mechanism [5]. Insulin resistance can lead to neurodegeneration through various pathways, including energy and metabolism deficits, oxidative stress, and the accumulation of neurotoxic substances [63]. Insulin resistance may also play a role in the development of Alzheimer's disease in patients with affective disorders [64]. The close relationship between type 2 diabetes mellitus (T2DM) and Alzheimer's disease is further supported by shared pathophysiological characteristics, such as impaired insulin sensitivity and amyloid β accumulation [65]. These findings highlight the potential for treating diabetes-related neurodegeneration and the need for further research in this area. Nonpharmacological interventions, particularly lifestyle modifications, are crucial for managing type 2

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diabetes and associated neurological conditions [66]. These interventions include physical exercise, dietary changes, and weight management, all of which have been shown to be effective in preventing and managing type 2 diabetes [67,68]. In addition to their impact on diabetes, these interventions also play a significant role in improving overall well-being and cognitive health [69].

The potential of antidiabetic drugs, such as metformin and thiazolidinediones, to promote neuronal survival and improve memory and cognition in patients with and without diabetes has been demonstrated [15]. This is particularly relevant given the increasing evidence of type 2 diabetes as a risk factor for Alzheimer's disease [70]. Glucagon-like peptide-1 (GLP-1) mimetics, a class of antidiabetic drugs, have shown promise in minimizing cell loss and possibly rescuing cognitive decline in models of neurodegenerative diseases [70]. The insulin signaling pathway, which is dysregulated in both type 2 diabetes and Parkinson's disease, is being explored as a potential target for disease treatment [71]. However, further research is needed to clarify the biochemical mechanisms of diabetic brain injury and to identify potential therapeutic approaches [72].

Exploring Molecular Targets: PPARs, PTP-1B, and GSK-3 Inhibitors

The molecular landscape of diabetes and potential therapeutic targets are complex and evolving fields. Peroxisome proliferator-activated receptors (PPARs), protein tyrosine phosphatase 1B (PTP-1B), and glycogen synthase kinase-3 (GSK-3) have been identified as key players in diabetes pathophysiology [73–76]. PPARs, in particular, have been highlighted as potential therapeutic targets due to their role in regulating lipid and glucose homeostasis [74]. PTP-1B, which negatively regulates insulin and leptin signaling, has also been identified as a promising target for enhancing insulin sensitivity and controlling body mass [73,76]. The potential of targeting these molecular entities to revolutionize diabetes management is a promising area for future research. The role of PPARs in regulating lipid metabolism, insulin, and triglycerides is crucial, and the development of PPAR agonists holds potential for therapeutic applications [77]. However, the safety concerns associated with these agonists, particularly dual-acting PPARγ/α agonists, are a significant challenge [78]. Despite these challenges, clinical evidence for the use of PPAR modulators in various health conditions is promising, with the potential for the future development of safer and more effective PPAR ligands [79]. The need for a balanced approach that retains efficacy while reducing potential side effects is emphasized [80].

The protein tyrosine phosphatase 1B (PTP-1B) has emerged as a promising target for treating diabetes and obesity, with a focus on developing small molecule inhibitors [81–83]. These inhibitors have the potential to enhance insulin and leptin action, thereby improving insulin sensitivity and glucose regulation. Recent advancements in the design of potent and selective PTP-1B inhibitors have been reported, with a focus on their safety and efficacy [84]. The development of these inhibitors holds promise for the future of diabetes treatment. Glycogen synthase kinase-3 (GSK-3) has emerged as a potential target for antidiabetic therapies, and various companies are investigating this topic further [85]. Inhibitors of GSK-3 have shown promise for promoting insulin-like effects and improving insulin resistance [86]. However, developing both effective and safe inhibitors is challenging because GSK-3 is involved in multiple physiological pathways [86]. Despite these challenges, the therapeutic potential of GSK-3 inhibitors in reshaping diabetes management is significant [87].

Future Directions of Neuropharmacology of Type 3 Diabetes

The neuropharmacology of type 3 diabetes presents promising avenues for furthering our comprehension and treatment of this intricate disorder. Future research in the neuropharmacology of type 3 diabetes should focus on discovering new therapeutic targets, improving treatment techniques, and deepening our understanding of the mechanisms that cause cognitive impairment in this group. Through the adoption of interdisciplinary cooperation and the use of advanced technology, we can provide a path for pioneering interventions that enhance outcomes and the overall quality of life for patients affected by type 3 diabetes. The following are important areas to investigate and study:

Targeted Therapies

The development of pharmaceutical therapies that specifically target and enhance insulin sensitivity while lowering neuroinflammation in the brain could be a vital approach. Potential pharmaceutical compounds that specifically target molecular pathways associated with type 3 diabetes, including insulin signaling cascades, tau protein phosphorylation, and amyloid-beta metabolism, have the potential to provide neuroprotective advantages and decelerate the advancement of Alzheimer's disease [17].

Precision Medicine Approaches

The utilisation of precision medicine approaches, which involve customising medications according to an individual's genetic, metabolic, and neuropathological profiles, has the potential to completely transform the management of type 3 diabetes. Tailored pharmacotherapies that consider an individual's specific risk factors, disease progression, and treatment response may result in improved therapeutic outcomes and enhanced clinical management of cognitive impairment in patients diagnosed with type 3 diabetes [88].

Neuroimaging Biomarkers

The development of advanced neuroimaging techniques to detect early biomarkers of brain insulin resistance and neurodegeneration in type 3 diabetes could help in the early identification and treatment of the condition [89]. By employing positron emission tomography (PET), magnetic resonance imaging (MRI), and functional MRI (fMRI), it is possible to identify changes in brain glucose metabolism, neuronal connections, and structural integrity. This can offer significant information about the advancement of diseases and the effectiveness of treatments [90].

Combination Therapies

Exploring the effectiveness of combination medicines that target several pathogenic pathways associated with type 3 diabetes may result in synergistic effects and enhanced clinical outcomes [91]. Combinations of insulin sensitizers, anti-inflammatory drugs, antioxidants, and neuroprotective chemicals may provide more effective therapeutic advantages compared to therapies targeting a single factor, and might assist address the complex and multifaceted character of type 3 diabetes [91,92].

Lifestyle Interventions

Investigating the therapeutic effects of lifestyle interventions, such as modifying food, engaging in physical activity, undergoing cognitive training, and practicing stress reduction techniques, on reducing cognitive decline linked to type 3 diabetes is a crucial field for future research [93]. Implementing lifestyle changes that support metabolic health, boost neural plasticity, and decrease neuroinflammation can be used alongside medication to optimise brain health in those who are at risk for or have type 3 diabetes [94].

Discussion and Conclusion

Diabetes mellitus, which is characterised by insulin resistance and abnormalities in insulin production, has a more complex history than only type 1 and type 2 diabetes. Novel insights into the genetic foundations of diabetes provide opportunities for tailored therapies, highlighting the heterogeneous character of this worldwide health concern. The emergence of type 3 diabetes, which connects diabetes with neurodegenerative diseases, particularly Alzheimer's disease, expands the narrative, shedding light on the intricate relationships between metabolic disorders and cognitive decline. The global prevalence of diabetes underscores the urgency of obtaining a comprehensive understanding of its various manifestations. While traditional classifications have laid the foundation, the advent of subgroups such as type 3 emphasizes the dynamic nature of diabetes science, demanding ongoing refinements for accurate diagnoses and targeted therapies. Standardizing definitions of diabetes remains a challenge, and the increasing diabetic population necessitates improved screening and management techniques.

The correlation between type 3 diabetes, commonly referred to as brain diabetes or AD, and Alzheimer's disease has garnered substantial interest in recent years. Recent findings indicate that insulin resistance in the brain, similar to what is observed in peripheral tissues in type 2 diabetes, plays a role in the onset and advancement of AD. Insulin resistance in neurons hampers the process of glucose metabolism, disturbs the functioning of neurons, and facilitates the occurrence of neurodegeneration. The aetiology of Alzheimer's disease is intimately associated with molecular and biochemical changes in type 3 diabetes. The abnormalities observed in this context encompass dysregulation of insulin signaling pathways, buildup of amyloid-β (Aβ) plaques, and hyperphosphorylation of tau protein. These abnormalities ultimately result in neuronal dysfunction and loss of synaptic connections. Furthermore, the presence of oxidative stress, inflammation, and mitochondrial dysfunction worsens the harm to neurons in the brains of individuals with Alzheimer's disease who also have type 3 diabetes.

Gaining insight into the fundamental causes of diabetic problems in Alzheimer's disease is crucial for the development of novel therapeutic approaches. Potential therapeutic strategies for type 3 diabetes-associated Alzheimer's disease involve targeting insulin signaling pathways, lowering the formation of Aβ, and boosting the clearance of amyloid. Moreover, therapies targeting the reduction of oxidative stress, inflammation, and mitochondrial dysfunction may provide neuroprotective advantages in Alzheimer's disease brains impacted by type 3 diabetes. Future research should prioritise the identification of early biomarkers for type 3 diabetes-related AD, the clarification of the role of vascular dysfunction in the development of AD, and the investigation of new therapeutic targets to prevent and treat vascular problems linked to type 3 diabetes. Collaboration among neuroscientists, endocrinologists, and clinicians is crucial for enhancing our comprehension of type 3 diabetes and creating efficient therapies to counteract its detrimental effects on neuronal function and survival in AD. The evolving field of neuropharmacology, coupled with advancements in antidiabetic medications, signals a paradigm shift in diabetes care. The focus on cognitive function and neuronal survival alongside glycaemic management reflects a holistic approach. Notably, the repurposing of antidiabetic medications for neurodegenerative diseases represents a promising frontier, revealing the intersection of diabetes and neurological research. The exploration of molecular and biochemical mechanisms elucidates the cellular intricacies underlying diabetic complications. Understanding the polyol pathway, altered cellular redox states, diacylglycerol formation, and advanced glycation end product generation is pivotal for revealing vascular dysfunction and oxidative stress. Targeting these pathways opens avenues for

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novel therapeutic strategies. Antidiabetic drugs, notably metformin, thiazolidinediones, and glucagon-like peptide-1 receptor-targeting compounds, offer promising prospects for neuroprotection. Their potential to enhance insulin signaling, protect against degeneration, and improve cognitive function is a beacon of hope for addressing neurodegenerative diseases, transcending their traditional roles in glycemic control.

Delving into molecular targets such as PPARs, PTP-1B, and GSK-3, the field is poised for transformation. These targets for reshaping diabetes management hold promise, albeit with challenges that demand a balanced approach. The evolving landscape of precision medicine in diabetes care anticipates breakthroughs in tailoring therapeutic strategies to individual needs. In the future, the concept of type 3 diabetes should be considered a focal point, and dedicated exploration of accurate diagnostic methods and targeted treatments is urgently needed. This paper serves as a catalyst for sustained exploration, interdisciplinary collaboration, and an unwavering commitment to pioneering the future of diabetes care. In illuminating the present, our aspiration is to shape a future where diabetes is met with precision, empathy, and innovative solutions.

Author Contributions

JKS and SG planned the thematic structure of the article and designed the overall layout. KV, KKS, KBN, JKS and SG performed the literature search and wrote the first draft of the manuscript. KV, JKS, NKJ, MPS, KKS, KBN and SG made significant contributions to the idea and design of the study. JKS, KKS, KBN and SG made final critical revisions to the paper to improve the intellectual content. All the authors contributed to editorial changes in the manuscript. All the authors read and approved the final manuscript. All the authors have participated sufficiently in the work and agreed to be accountable for all the aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest. Shampa Ghosh and Jitendra Kumar Sinha are serving as the Guest editors of this journal. We declare that Shampa Ghosh and Jitendra Kumar Sinha had no involvement in the peer review of this article and have no access to information regarding its peer review.

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