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Mechanisms and Frontiers of Treatment for Diabetes-Related Epilepsy

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Abstract

Diabetes is a clinically common metabolic disease characterized primarily by a long-term state of high blood sugar. It not only leads to multi-organ dysfunction throughout the body but also significantly increases the risk of secondary epilepsy. However, there are still controversies and deficiencies regarding the various mechanisms of occurrence and clinical treatment methods for diabetes-related secondary epilepsy. This article systematically reviews the pathogenesis between diabetes and secondary epilepsy, including neurotransmitter imbalance, metabolic disorders, cerebrovascular lesions, and energy deficiency. Current pharmacological treatment methods are discussed, highlighting the neuroprotective potential of antidiabetic drugs and the safety of new antiepileptic drugs. In addition, emerging non-pharmacological intervention methods, such as neuromodulation and gene therapy, are also discussed, aiming to provide a theoretical basis and new ideas for clinical diagnosis and treatment, and to promote further optimization of clinical treatment strategies.

Keywords

Diabetes, Secondary Epilepsy, Pathological Mechanism, Treatment Progress

1. Introduction

Diabetes mellitus (DM) is a metabolic disease characterized by chronic hyperglycemia. In recent years, the global prevalence has continued to rise, becoming an important public health challenge. Its pathological core mainly includes defects in insulin secretion (commonly seen in type 1 diabetes) or insulin resistance (as seen in type 2 diabetes). Poor long-term blood glucose control can lead to multi-system damage, with notable involvement of the nervous system, which has become a

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major focus in clinical and research settings [1] [2]. Diabetic patients often experience cognitive decline, peripheral neuropathy, and abnormalities in brain structure and function, which significantly reduce their quality of life and long-term prognosis [3] [4]. Additionally, DM is closely related to cerebrovascular diseases. It may disrupt the integrity of the blood-brain barrier, exacerbate oxidative stress and inflammatory responses, thereby promoting neurodegenerative processes and ultimately increasing the risk of related neurological diseases [5].

Secondary epilepsy, as a common neurological complication in diabetic patients, has a complex and diverse pathogenesis. On one hand, acute and severe disturbances in blood glucose metabolism (such as non-ketotic hyperglycemia or hypoglycemia) can directly trigger acute symptomatic seizures. On the other hand, prolonged hyperglycemic states can lead to neurotransmitter system imbalance, intracellular metabolic disorders, chronic inflammation activation, and microvascular lesions. These factors interact synergistically, making brain tissue more susceptible to damage and increasing neuronal excitability, ultimately resulting in chronic and recurrent epilepsy [6] [7]. However, such seizures are often unpredictable and recurrent, which not only exacerbates the patient's anxiety and psychological burden but also severely impacts their work efficiency and social functions, thereby reducing overall quality of life. Additionally, the burden of epilepsy affects not only the individual and their family but can also lead to excessive consumption of medical resources and increase socio-economic pressure.

In recent years, with experiments and clinical evidence from scholars in various regions, the association between DM and secondary epilepsy, as well as its underlying mechanisms, has gradually become clearer, and corresponding indirect treatment strategies have been continuously proposed. Currently, more focus is being placed on intervention methods related to diabetes-associated neurological damage, such as regulating glutamatergic neurotransmission, reducing oxidative damage, or repairing blood-brain barrier function, all of which are considered potential therapeutic targets [5] [8]. Although these methods provide important ideas for the overall management of diabetes-related neuropathy, there is still a lack of systematic and standardized treatment plans for secondary epilepsy directly induced by DM in clinical practice. Therefore, more clinical research is needed to comprehensively reveal its pathophysiological network and develop more precise and effective intervention measures to ultimately improve the quality of life for patients. This article aims to explore the potential mechanisms by which DM induces secondary epilepsy and the latest treatment progress, intending to provide theoretical basis and innovative ideas for related scientific research and clinical practice.

2. The Mechanism of Secondary Epilepsy

2.1. Theory of Neurotransmitter Imbalance

Neurotransmitters are a class of crucial chemical messengers in the nervous system. Synthesized and released by neurons, they can specifically bind to receptors on the postsynaptic membrane, thereby activating or inhibiting the next-level neurons,

and achieving precise transmission of neural signals. Maintaining the dynamic balance of neurotransmitters is of great significance for the normal functioning of the central nervous system [9]. In the pathogenesis of epilepsy, the excitatory neurotransmitter glutamate and the inhibitory neurotransmitter γ-aminobutyric acid (GABA) play important roles. Once the levels of the two are imbalanced, it will directly disrupt the excitatory-inhibitory balance of neural signals, significantly lowering the threshold for seizures and inducing epilepsy. This imbalance is more pronounced in diabetic patients. Studies have found that the expression of glutamate receptors in the brains of diabetic patients is significantly upregulated, especially the GluN2B subtype of the NMDA receptor, which has a high calcium ion permeability. Its excessive activation can lead to calcium overload, subsequently inducing mitochondrial dysfunction, excessive production of reactive oxygen species, and excitotoxic responses, ultimately resulting in neuronal damage and abnormal synaptic remodeling. At the same time, the phosphorylation level of the AMPA receptor GluA1 subunit is enhanced, further increasing the sensitivity and response intensity of the postsynaptic membrane to glutamate, causing excessive excitation of the neural network and lowering the seizure threshold. For instance, Mohamed MAE *et al.* found in a rat model of DM combined with epilepsy that the levels of glutamate increased, GABA levels decreased, and the expression of glutamate receptor subtypes was significantly upregulated, accompanied by a decline in GABAergic inhibitory function, collectively promoting increased susceptibility to epilepsy [10]. On the other hand, defects in the GABAergic inhibitory system also play an important role in diabetes-related epilepsy. The synthesis of GABA is highly dependent on the activity of glutamate decarboxylase (GAD). The pathological environment of DM includes persistent hyperglycemia, insulin resistance, and the accumulation of advanced glycation end products, which can trigger endoplasmic reticulum stress and oxidative damage, directly inhibiting GAD activity. Especially in patients with type 1 DM, autoimmune antibodies (such as anti-GAD65 antibodies) specifically attack and damage the structure of GAD, reducing its catalytic capacity. Abnormal insulin signaling pathways further affect the normal expression and function of GAD, possibly by altering intracellular signaling and gene expression regulation, weakening GABA's synthesis capability. Impaired GABA synthesis leads to weakened inhibitory neurotransmission, increasing the risk of uncontrolled neuronal firing. Shinichiro Sano *et al.* reported a case of a 17-year-old male who developed anti-GAD antibody-related neurological symptoms following allogeneic hematopoietic stem cell transplantation and type 1 DM. The patient's serum and cerebrospinal fluid showed significantly elevated levels of anti-GAD antibodies, along with marked hyperglycemia. After immunosuppression and insulin treatment, his neurological symptoms alleviated, and blood sugar was controlled, but the antibodies persisted. This case not only illustrates the correlation between anti-GAD antibodies, DM, and its neurological complications but also suggests that intervening in the GABA synthesis pathway may have considerable clinical application potential in treating related epilepsy [11].

2.2. Theory of Metabolic Disorders

In diabetic patients, long-term hyperglycemia can trigger disturbances in glucose metabolism in the brain. These disturbances affect the energy supply and metabolic balance of neurons, significantly increasing the risk of epilepsy. Hyperglycemia and insulin resistance hinder aerobic metabolism of glucose, forcing neurons to switch to anaerobic glycolysis, leading to a massive accumulation of lactic acid. The accumulation of lactic acid not only causes intracellular acidosis, inhibits mitochondrial function, and exacerbates the energy crisis, but also disrupts ionic homeostasis, directly affecting the ability of astrocytes to reuptake glutamate. Moreover, the combination of energy deficiency and acidosis weakens the function of potassium-chloride cotransporters on neuronal membranes, resulting in the accumulation of chloride ions within the cell, which reverses inhibitory GABAergic signals into depolarizing excitatory signals, significantly lowering the seizure threshold. Research by Shuang Tian *et al.* shows that lactic acid levels in the cerebrospinal fluid of diabetic patients are elevated, indicating metabolic disturbances and hypoxic conditions in the brain, which may further increase neuronal excitability and promote the occurrence of epilepsy [12]. Metabolic abnormalities not only lead to insufficient energy supply but also disrupt intracellular calcium ion homeostasis. Calcium ions, as important second messengers within neurons, exhibit dysregulation under the dual influences of endoplasmic reticulum stress and oxidative stress: uncontrolled release from endoplasmic reticulum calcium stores, excessive activation of membrane calcium channels, and decreased activity of calcium pumps all contribute to intracellular calcium overload. Persistently high levels of calcium not only activate various calcium-dependent enzymatic reactions, promoting the release of glutamate and inhibiting GABAergic transmission but also induce excitotoxicity, damaging neurons and synaptic structures, progressively driving the formation of abnormal discharge networks. Sakshi Saini *et al.* confirmed through animal experiments that the activity of key glycolytic enzymes in the brains of diabetic rats is reduced, and glucose metabolism efficiency is decreased, further impairing the functional stability of neurons, indicating that metabolic disturbances affect the central system far beyond abnormal blood sugar levels and further promote the onset of epilepsy [13]. Additionally, DM is often accompanied by lipid metabolism disorders, particularly the abnormal elevation of free fatty acids and oxidized lipid levels, which continuously activate microglia and astrocytes in the brain. These activated glial cells release a large number of inflammatory factors centered on IL-1β and TNF-α, forming a sustained chronic inflammatory environment in the brain. This inflammatory state damages neurons through multiple pathways: on one hand, inflammatory factors directly upregulate the activity of glutamate receptors in neurons, enhancing glutamatergic excitatory transmission while inhibiting the function of GABAergic interneurons, thereby disrupting the critical excitatory-inhibitory balance in neural networks; on the other hand, inflammatory attacks induce mitochondrial dysfunction and oxidative stress, leading to an energy crisis and structural damage in neurons. Ul-

timately, this cascade of damage driven by lipid abnormalities and executed by inflammatory factors significantly reduces the stability of neuronal networks, greatly lowering the threshold for synchronized abnormal discharges, thereby clearly promoting the occurrence and development of secondary epilepsy.

2.3. Cerebrovascular Pathology Theory

DM, as a global disease, not only affects the cardiovascular system, kidneys, and retina but also profoundly damages the central nervous system through multiple mechanisms, significantly increasing the risk of secondary epilepsy. In this process, diabetes-induced cerebrovascular lesions are considered a key pathological link between the two diseases. By altering the structure and function of brain tissue, it lays a pathological foundation for the formation of abnormal discharge networks and epileptic foci. Under prolonged hyperglycemia, endothelial cells are damaged, leading to increased permeability of the blood-brain barrier. The impairment of this important physiological barrier allows inflammatory cells and various inflammatory mediators from peripheral circulation to more easily invade brain tissue, activating microglia and astrocytes, thereby triggering a local immune-inflammatory cascade that releases a large number of pro-inflammatory cytokines such as IL-1β and TNF-α. This inflammatory microenvironment not only directly damages neurons and synapses but also upregulates glutamate receptor expression while inhibiting GABAergic interneuron function, thus overall increasing the abnormal excitability of neural networks and susceptibility to epilepsy [14]. It is noteworthy that the persistent inflammatory response is not only a triggering factor for epilepsy but is also considered an important mechanism for the development of drug-resistant epilepsy in some cases. Moreover, the local structural remodeling of brain tissue caused by cerebrovascular lesions is also a critical factor in the formation of epileptic foci. Diabetes-related cerebral infarction and diffuse microvascular disease can lead to ischemic necrosis of brain tissue, which in turn triggers reactive gliosis and scar formation. These structural changes disrupt the connections of normal neurons, prompting surviving neurons to form abnormal connections. At the same time, their electrophysiological characteristics, such as ion channel expression and resting membrane potential, also change, ultimately transforming into a highly autonomous excitability point of abnormal electrical activity, that is, a typical epileptic focus. In epidemiological studies, a study by Maria Stefanidou *et al*. with an average follow-up of 19 years showed that populations with risk factors for cerebrovascular lesions (such as hypertension and DM) have a risk of developing epilepsy several times that of the general population. This data clearly reveals the significant correlation between cerebrovascular damage and the incidence of epilepsy [15]. As a triggering factor for cerebrovascular lesions, DM indirectly increases the risk of epilepsy. Coincidentally, an analysis by Kunihiko Araki *et al*. on 36 epilepsy patients undergoing hemodialysis found that the vast majority of patients presented with focal seizures, with electroencephalogram features characteristic of focal slow waves and abnor-

mal discharges consistent with structural brain damage, strongly suggesting that the source of seizures lies in structural changes such as ischemic necrosis of brain tissue and gliosis caused by cerebrovascular lesions. These changes collectively form a pathological network prone to abnormal discharges [16]. As a core risk factor leading to atherosclerosis and microvascular disease, DM indirectly and significantly increases the overall risk of epilepsy by promoting cerebrovascular damage.

2.4. Theory of Energy Deficiency

The maintenance of brain energy metabolism is crucial for the functioning of the central nervous system. Although the brain accounts for only about 2% of body weight, it consumes as much as 20% of the body's energy, primarily relying on glucose as the energy source to support a series of high-energy-consuming activities such as neuronal firing, synaptic information transmission, and maintaining ion gradients inside and outside the cell membrane. In patients with DM, the impairment of insulin signaling pathways is a key factor leading to a brain energy crisis. Insulin not only regulates blood sugar in peripheral tissues but also plays a critical role in the central nervous system. It enhances the uptake and utilization of glucose by neurons and glial cells through insulin receptors distributed in brain regions such as the hippocampus, hypothalamus, and cortex, while also regulating synaptic plasticity and cognitive function [17] [18]. When DM induces insulin resistance in the brain, the regulatory network is disrupted. The efficiency of glucose uptake by brain cells decreases, leading to insufficient energy supply for neurons [19] [20]. This not only directly impairs cognitive function and neurotransmission but also induces oxidative stress and chronic neuroinflammation, forming a vicious cycle that continuously damages neural tissue and ultimately promotes the occurrence of seizures. Diabetes can lead to mitochondrial dysfunction through various pathways. Neurons are highly dependent on mitochondria to efficiently produce ATP through oxidative phosphorylation to maintain stable membrane potential and normal conduction of action potentials. However, chronic hyperglycemia and metabolic disorders associated with DM can impair the activity of mitochondrial respiratory chain complexes and inhibit ATP production. The energy shortage makes it difficult for neurons to maintain normal ion pump function, decreases cell membrane stability, and lowers the threshold for tolerance to excitatory stimuli, thus making abnormal discharges more likely [21]. Research by Carrera-Bastos P *et al.* indicates that metabolic reprogramming associated with diabetes (such as the Warburg effect) can lead to alterations in mitochondrial energy metabolism pathways, forcing neurons to rely more on the inefficient glycolytic pathway for energy supply, further exacerbating the dilemma of energy utilization [22]. Scholars such as Miljanovic N found in relevant animal models that mitochondrial morphology in the brain tissue of diabetic rats exhibited significant abnormalities, characterized by structural swelling and blurred or broken cristae. This structural damage severely impairs the

oxidative phosphorylation process. The lack of sufficient ATP not only weakens the ability of neurons to maintain resting membrane potential but also hinders the normal synthesis and vesicular release of neurotransmitters (such as GABA), leading to diminished inhibitory function. Ultimately, the balance between excitation and inhibition is completely disrupted, resulting in an overall abnormal increase in the excitability of neural networks, significantly increasing susceptibility to seizures [23].

In summary, DM can lead to the occurrence of secondary epilepsy through various mechanisms. The core issue regarding neurotransmitter imbalance lies in excessive glutamatergic excitation and insufficient GABAergic inhibition, with corresponding intervention targets including the regulation of NMDA/AMPA receptor function and enhancement of GABA synthesis. For metabolic disorders involving lactic acidosis, calcium homeostasis imbalance, and neuroinflammation, treatment strategies focus on correcting acidosis, regulating calcium channels, and inhibiting inflammatory factors such as IL-1β. Furthermore, cerebrovascular lesions cause structural lesions by disrupting the blood-brain barrier and triggering glial proliferation, and potential therapies need to focus on barrier repair and antiproliferation. Lastly, energy deficiency arises from brain insulin resistance and mitochondrial dysfunction, making the improvement of central insulin signaling and mitochondrial metabolism a key breakthrough. These four factors together form a network, and future research should further explore the dynamic interactions between these mechanisms to optimize clinical applications, enabling more effective stabilization of neural networks and control of seizures.

3. Therapeutic Drugs

3.1. Antidiabetic Medications

Traditional hypoglycemic drugs have always played a central role in the DM management system. Recent studies have found that some medications not only effectively control blood sugar levels but may also exert neuroprotective effects through various mechanisms, reducing the risk of seizures. Metformin, as a classic oral hypoglycemic agent, has recently been found to have a potential role in reducing seizure risk. It activates the AMPK signaling pathway, improves energy metabolism in brain tissue, enhances mitochondrial function, and alleviates oxidative stress, thereby increasing neuronal stability and the ability to prevent abnormal discharges. Additionally, it suppresses microglia-mediated neuroinflammation, reduces the activity of inflammatory pathways such as NLRP3 inflammasome, and decreases the release of pro-inflammatory factors. At the same time, by inducing autophagy, it helps eliminate damaged organelles and misfolded proteins within neurons, maintaining intracellular homeostasis. Research also suggests that it may further optimize the neural microenvironment by regulating the mTOR signaling pathway and balancing GABA and glutamate levels, comprehensively exerting its anti-epileptic potential [24]. Aayushi Nangia *et al.* have shown that metformin can also promote the production of neuroprotective metabolites by regulating gut mi-

crobiota, expanding its neuroregulatory mechanisms from the gut-brain axis perspective [25].

Sodium-glucose co-transporter 2 inhibitors (SGLT2i), as a newer type of hypoglycemic medication, not only demonstrate cardiac and renal protective effects but also show potential anticonvulsant effects. They achieve this by inhibiting renal glucose reabsorption and promoting urinary glucose excretion, which comprehensively improves metabolic disorders and chronic inflammatory states in the body, thereby alleviating oxidative stress and inflammatory burdens in brain tissue. At the same time, SGLT2 inhibitors promote the generation of ketone bodies in the body, providing the brain with a more efficient and cleaner alternative energy source, enhancing neuronal energy adaptability and electrical stability under conditions of glucose metabolism disturbances. The anti-inflammatory and autophagy-promoting effects of these drugs also extend to the central nervous system, not only inhibiting NLRP3 inflammasome activation but also indirectly optimizing the neural environment by improving cerebral blood flow and microcirculation. The potential anticonvulsant effects of these drugs are not due to a single pathway but rather the concentrated manifestation of their multiple effects in metabolic regulation, energy substitution, anti-inflammation, and vascular protection within the nervous system. Marisa Mekkittikul *et al*. discovered through stable isotope tracing technology that the SGLT2 inhibitor dapagliflozin can specifically restore the glucose metabolic flux in the synaptic body. This effect maintains TCA cycle homeostasis and synaptic energy supply, confirming its mechanism for improving brain energy deficits from the perspective of synaptic metabolism [26]. Similarly, GLP-1 receptor agonists have also shown the ability to regulate energy metabolism through the central nervous system and possess potential neuroprotective functions [27]. These drugs not only improve brain glucose uptake and mitochondrial function but also exhibit potential anti-neuroinflammatory and antioxidant properties. A retrospective cohort study by Ching-Yang Cheng *et al*. indicated that the incidence of epilepsy in patients using GLP-1 receptor agonists was significantly lower than that in those using dipeptidyl peptidase-4 inhibitors, suggesting that they have neuroprotective effects independent of their hypoglycemic actions [28].

Strict blood glucose management plays an important protective role for the nervous system of patients with diabetes. It can effectively avoid acute symptomatic seizures caused by severe fluctuations in blood glucose levels (especially hypoglycemia) [29]. At the same time, long-term stable blood glucose control also helps delay the progression of chronic neurological damage such as diabetic cerebrovascular disease, thereby fundamentally reducing the risk of developing chronic epilepsy in the future. In this process, some hypoglycemic medications show unique advantages, such as metformin, SGLT2 inhibitors, and GLP-1 RAs, which, due to their multi-mechanism neuroprotective effects beyond glucose-lowering, provide a safer and more effective treatment strategy for patients with diabetes complicated by epilepsy.

3.2. Antiepileptic Drugs

In the clinical treatment of diabetic patients with secondary epilepsy, accurately assessing and avoiding drug interactions is a core aspect to ensure efficacy and safety. The pharmacokinetic interactions between enzyme-inducing AEDs (eiAEDs) and oral hypoglycemic agents are particularly critical. eiAEDs (such as carbamazepine, phenytoin, phenobarbital, and oxcarbazepine) significantly accelerate the clearance of various drugs metabolized through the same pathways by continuously activating the liver cytochrome P450 enzyme system (especially CYP3A4 and CYP2C9) and the uridine diphosphate glucuronosyltransferase (UGT) system, directly leading to reduced blood concentrations and efficacy of co-administered oral hypoglycemic agents. Sulfonylurea insulin secretagogues (such as glibenclamide, glimepiride, and glipizide), as substrates of CYP2C9, are most significantly affected, with their hypoglycemic efficacy potentially diminished due to accelerated metabolism, forcing clinicians to increase dosages to maintain blood sugar targets, which in turn may increase the risk of severe hypoglycemia due to fluctuations in drug concentration. Additionally, the efficacy of thiazolidinediones (such as pioglitazone, which is metabolized by CYP2C8) may also be weakened, and even insulin, which is not directly metabolized by liver enzymes, may have its dosing and body sensitivity become more difficult to stabilize due to pharmacodynamic interference. It is worth noting that some non-enzyme-inducing AEDs are not entirely safe either; for instance, sodium valproate, which has potential enzyme-inhibiting effects, may also cause abnormal blood glucose levels by slowing the metabolism of certain medications.

Currently, for diabetic patients diagnosed with chronic epilepsy, traditional antiepileptic drugs such as carbamazepine and valproate remain the core treatments in clinical practice. However, when these drugs are used in diabetic patients, careful consideration must be given to their metabolism and potential effects on blood glucose levels. Valproate can cause hyperammonemia and liver function abnormalities; some studies have also reported that it can interfere with glucose and lipid metabolism, which may further increase the metabolic burden on diabetic patients [30]. Carbamazepine, as a liver enzyme inducer, can accelerate the metabolism of various medications such as insulin and oral hypoglycemic agents, leading to blood glucose fluctuations and even a risk of hypoglycemia. Therefore, when using these traditional drugs in diabetic patients, close monitoring of blood glucose levels and liver and kidney function is necessary, and medication adjustments should be made promptly based on the test results.

Compared to traditional medications, second-generation antiepileptic drugs such as lamotrigine and levetiracetam are gradually becoming a better choice for the treatment of epilepsy in diabetic patients due to their superior safety profile and fewer drug interactions. Lamotrigine, as a use-dependent blocker of voltage-gated sodium channels, preferentially targets neurons with high-frequency discharges, binding to sodium channels in their activated or inactivated states, thereby delaying their recovery process, reducing the influx of sodium ions, decreasing

neuronal excitability, and stabilizing membrane potential, which suppresses the initiation and spread of abnormal discharges at the source. Levetiracetam, on the other hand, exerts its effects through its high selectivity for binding to the synaptic vesicle protein SV2A, which is involved in regulating the release of neurotransmitters. Its binding can stabilize the exocytosis of synaptic vesicles, reducing the pathological release of excitatory transmitters such as glutamate, and inhibiting the abnormal synchronized activities of neural networks, demonstrating broad-spectrum antiepileptic properties. Additionally, levetiracetam is primarily excreted through the kidneys and does not heavily rely on liver metabolism, thus posing a lower risk of drug interactions, making it particularly suitable for elderly patients or those with multiple comorbidities. Clinical studies have shown that it has a good safety profile and reliable efficacy in elderly epilepsy populations [31]. Lamotrigine also possesses pharmacokinetic advantages, having minimal effects on cognitive function and a low metabolic burden on the liver, making it very suitable for patients needing long-term medication and with metabolic diseases. A long-term medication tracking analysis by Atmaram Bansal and others among the Indian population indicates that the clinical usage rates of lamotrigine and levetiracetam are steadily increasing, reflecting recognition of their efficacy and safety characteristics [32].

At the beginning of the 21st century, third-generation antiepileptic drugs such as lacosamide and brivaracetam were successively launched into the market and gradually applied in clinical practice. Unlike the first two generations of antiepileptic drugs, third-generation medications achieve precise intervention in pathological mechanisms. For instance, lacosamide exerts its antiepileptic effect through a unique mechanism that selectively enhances the slow inactivation state of voltage-gated sodium channels, demonstrating a high frequency dependence that can accurately suppress pathological high-frequency discharges during seizures while minimally affecting normal neural activity [33]. Brivaracetam, on the other hand, binds with ultra-high affinity to the synaptic vesicle protein SV2A, regulating neurotransmitter release more efficiently. This fundamental difference in mechanism allows for effective seizure control while maximizing the reduction of interference with normal brain function, resulting in fewer central side effects such as cognitive impairment. Moreover, most drugs (such as lacosamide) are not metabolized by liver CYP450 enzymes, presenting a very low risk of drug interactions, making them more suitable for patients with multiple comorbidities. Overall, third-generation drugs represent a shift in the therapeutic paradigm from broad control to precise regulation, offering more effective and safer treatment options for patients with refractory epilepsy.

Currently, the combination therapy of hypoglycemic drugs and antiepileptic drugs has become a new strategy for managing diabetes-related epilepsy. This combination not only helps achieve dual control of blood sugar and epilepsy seizures but also reduces the side effects associated with high doses of single medications through complementary drug actions. Choosing new antiepileptic drugs

that do not interfere with blood sugar can avoid exacerbating the metabolic burden of diabetes; at the same time, good blood sugar control can help improve the excitability threshold of neurons and reduce seizures. When formulating an antiepileptic treatment plan, the specific situation of the patient should be comprehensively considered, including the duration of diabetes, blood sugar control level, complications, types of seizures, and drug tolerance. Since diabetic patients often have multiple medications, rational drug selection to reduce interactions and decrease liver and kidney burden is crucial for improving treatment adherence and effectiveness. Future research could further explore the multi-faceted protective mechanisms of antiepileptic drugs in diabetic neuropathy, paving new paths for personalized treatment of diabetes-related epilepsy.

4. Latest Treatment Plan

In addressing the clinical issue of diabetes-related secondary epilepsy, various emerging non-drug therapies, in addition to pharmacological interventions, are demonstrating broad application prospects, together forming a multi-level treatment system that ranges from neural circuit regulation to molecular repair.

Neural modulation technology, as a type of non-invasive or minimally invasive physical regulation method, has recently been found to effectively utilize external energy or electrical signals to modulate the function and plasticity of abnormal brain networks. Among these, transcranial magnetic stimulation (TMS) uses magnetic fields to induce electric fields in the cortex, allowing for non-invasive regulation of the excitability of specific brain regions. Low-frequency repetitive TMS can induce effects similar to long-term depression (LTD) in the target area, persistently reducing the excitability and synchronization tendency of local neurons, thereby inhibiting epileptic-like activity. Of course, the effects of TMS may not be limited to neurons; it can also regulate the function of astrocytes. Astrocytes play a key role in maintaining neurotransmitter balance and brain energy metabolism, and their dysfunction is closely related to diabetic brain injury and epilepsy susceptibility. By modulating the balance of glutamate and GABA and potentially improving the synaptic microenvironment, TMS holds promise for assisting in the restoration of excitatory-inhibitory homeostasis at the cellular interaction level, while precise regulation targeting glial cells may become a new therapeutic target in the future [34].

Another mature technology is vagus nerve stimulation (VNS). Its mechanism of action in treating epilepsy does not directly target the brain lesion, but rather stimulates the peripheral vagus nerve through electrodes implanted in the neck. The stimulation signals are relayed through structures such as the solitary nucleus and locus coeruleus, and are widely projected to the thalamus, cortex, and limbic system, enhancing inhibitory tension across the brain by promoting the release of inhibitory neurotransmitters such as norepinephrine, serotonin, and GABA, while possibly inhibiting the excessive excitation of glutamate, thus raising the threshold for epileptic seizures [35]. Additionally, VNS has been found to have effects in

regulating neuroinflammation and promoting the expression of neurotrophic factors, suggesting that its efficacy may partly stem from long-term neuroprotection and network remodeling, rather than solely from immediate electrophysiological inhibition [36].

For drug-resistant epilepsy, deep brain stimulation (DBS) provides a more direct intervention method. Its mechanism is not simply excitation or inhibition, but rather interferes with and resets pathological neural networks through various means. When high-frequency electrical stimulation acts on key nodes such as the anterior thalamic nucleus, it may exert functional inhibition on overactive neuronal groups through effects like depolarization blockade or synaptic depletion, thereby interrupting the propagation of abnormal oscillations in the circuit, achieving the goal of controlling seizures [37]. At the same time, DBS pulses can effectively modulate pathological neural oscillations and synchronized activities, thus blocking the propagation of abnormal discharges in key circuits. Modern bioelectromedicine utilizes neural implant devices, combined with neural and non-neural biomarkers, to achieve closed-loop feedback control, thereby personalized adjusting stimulation parameters to improve treatment efficacy and safety [38]. With advancements in neural implant technology and neural activity decoding technology, DBS is expected to become an important treatment method for diabetes-related epilepsy.

Given that oxidative stress and chronic inflammation, which are prevalent in the diabetic brain environment, are significant contributing factors to the occurrence of epilepsy, targeted antioxidant and anti-inflammatory combination therapies have also received much attention. For instance, the antioxidant alpha-lipoic acid not only scavenges free radicals but also activates the AMPK signaling pathway to improve cellular energy metabolism, while inhibiting inflammation-mediated damage processes such as matrix metalloproteinase 9 (MMP-9). Thus, while improving diabetic peripheral neuropathy, it may also help stabilize neuronal excitability [39]. Combining such drugs with traditional antiepileptic therapies is expected to achieve better treatment outcomes by improving the brain environment and increasing neuronal stability.

In the more advanced field of restorative therapies, stem cell therapy and gene therapy provide new directions for fundamentally reversing nerve damage. It should be noted that such strategies currently primarily target rare genetic syndromes characterized by the coexistence of diabetes and epilepsy caused by certain single-gene defects (such as diseases associated with TMEM167A and TARS2 gene mutations), rather than common type 2 diabetes or secondary epilepsy induced by autoimmune type 1 diabetes. For these special hereditary diseases, gene therapy aims to halt the disease progression by correcting pathogenic gene mutations; stem cell therapy is dedicated to the directed differentiation and transplantation of functional cells to replace damaged neurons or glial cells, rebuild neural circuits, and restore inhibitory regulation [40] [41]. Although most current research is still in the preclinical or early clinical trial stages with limited applicability, these

breakthrough strategies signify a shift in disease treatment models from symptom control to precise repair, laying the scientific foundation for future applications in a broader range of neurological complications.

5. Summary and Outlook

Diabetes-induced secondary epilepsy, as a complex neurological complication, poses significant challenges in clinical diagnosis and treatment due to its diverse and interactive pathogenesis. Current research indicates that the onset of this condition is not driven by a single factor but rather results from the synergistic effects of multiple pathways, including neurotransmitter imbalance, metabolic disorders, cerebrovascular lesions, and energy metabolism defects. This understanding of multifactorial interactions necessitates therapeutic strategies that go beyond single-target approaches, emphasizing a more systematic and comprehensive approach to rationally utilize hypoglycemic agents and antiepileptic drugs to control disease progression, reduce seizure frequency, and mitigate severity. Concurrently, the flexible application of neuromodulation techniques and other interventions provides patients with individualized, comprehensive treatment support, significantly enhancing clinical efficacy and quality of life. However, current studies exhibit certain discrepancies and controversies in mechanism elucidation and therapeutic efficacy evaluation. Some research emphasizes the dominant role of metabolic factors in pathogenesis, while others focus on neurotransmitter dysfunction. Similarly, in terms of therapeutic strategies, some emerging therapies remain in the preliminary exploration phase and lack large-scale clinical validation. Therefore, we should maintain a cautious attitude, promote multidisciplinary collaboration and research, and gradually develop more refined treatment strategies by integrating diverse data and clinical experience. In the future, in-depth exploration of the molecular and cellular mechanisms underlying diabetes-associated epilepsy remains a key research focus. Utilizing modern molecular biology, neuroimaging, and big data analytics technologies, it is anticipated that more potential pathogenic targets and biomarkers will be identified, providing a basis for early diagnosis and precision therapy. Concurrently, a deeper understanding of the impact of individual variations—such as age, gender, neurobiochemical markers, and brain network characteristics—should be pursued to advance personalized treatment strategies. This will help maximize therapeutic efficacy while minimizing adverse effects. In summary, the research and clinical management of diabetes-associated epilepsy are in a phase of continuous progress and optimization. By integrating basic and clinical research findings, fostering multidisciplinary collaboration, and promoting the development of personalized precision medicine, it is hoped that this complex disease can be more effectively controlled in the future, thereby improving patient outcomes and quality of life.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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