Review Article

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Antidiabetics have Beneficial Effects on Epileptic Seizures in Diabetic Patients: A Narrative Review

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ABSTRACT

Several studies have reported the association of diabetes mellitus with epilepsy. With respect to the management of diabetes–epilepsy patients, these studies pointed out the beneficial effects of the ketogenic diet. Ketogenic diets may have antiepileptic properties as the utilization of ketone bodies in the brain instead of glucose delays or inhibits the degradation of γ-aminobutyric acid (GABA) transaminase, and thereby enhances the concentration of GABA. By restoring normal intracerebral GABA levels and reducing the cerebral inflammation linked to epilepsy, metformin is useful in preventing seizures. Sitagliptin has a positive impact on epilepsy by acting as an antioxidant and restoring normal GABA levels. Weight gain is a well-known side effect of anti-seizure medications. Sodium valproate can cause dyslipidemia and inhibits glucose transporter-1 in the brain, putting patients with epilepsy and diabetes at risk of developing atherosclerosis. Cellular stress in diabetes and epilepsy induces autophagy and activates lipid peroxidation, which leads to ferroptosis. It's worth looking at how ferroptosis and autophagy contribute to the etiology of diabetes and epilepsy, as well as how antiepileptics and antidiabetics alter these pathological processes. Therefore, it was worth performing a narrative-review on the effects of antiepileptics on diabetes, the effect of antidiabetics on epilepsy, as well the net results of antiepileptic–antidiabetic interactions in those patients.

Keywords: Epilepsy, Antidiabetes, Antiepileptics, Autophagy, Ferroptosis

1. Introduction

Chronic epilepsy is associated with a number of systemic autoimmune diseases, including diabetes mellitus [1]. It has been reported that the odds ratio of the association of epilepsy with autoimmune disease is 3.8 [2]. Type 1 Diabetes (T1D) is an autoimmune disease, and patients are at risk of having seizures three times greater than healthy subjects [2]. Refractory epilepsy and epilepsy of unknown origin are more common clinical findings in T1D [3]. Both T1D and epilepsy showed genetic predisposition, a positive test of anti-glutamic decarboxylase antibodies, derangement of glucose metabolism, and cerebral ischemia [4].

Type 2 diabetes (T2D) patients are at risk of developing epilepsy, as a population-based study demonstrated a hazard ratio of 1.44 [5]. Both T2D and epilepsy are running in a vicious cycle mediated by obesity as a comorbid factor (Figure 1) [6]. Moreover, mitochondrial dysfunction is a pathological landmark of obesity, epilepsy and T2D, and it explains the association between these diseases [6]. In the management of epilepsy, different modalities are used including pharmacological intervention, ketogenic diet, vagal stimulation, surgical intervention, *etc.* Each of these modalities may be affected by the metabolic derangement of diabetes and/or interactions with the antiepileptics or sometimes named antiseizure medications (ASM). Furthermore, autophagy and ferroptosis pathways were altered in both epilepsy and diabetes mellitus. Some ASM and antidiabetic drugs (ADDs) have been shown to have considerable impacts on autophagy and ferroptosis, which may be beneficial or detrimental in patients with coexisting conditions.

2. The Effects of Ketogenic Diet

The ketogenic diet is considered in the management of epilepsy to control the occurrence of seizures and improve the efficacy of ASM. The constituents of the diet are high fat, sufficient protein, and low carbohydrate contents, which should be no more than 10% [7]. The principle of this diet is to shift the energy sources from glucose metabolism towards ketones production, e.g., acetoacetate and β-hydroxybutyrate from fat metabolism, and this energy biodirection is simulating the fasting state. Ketogenic diets are not free from adverse reactions, including metabolic acidosis, dehydration, lethargy, behavioral disturbances, and systemic infections [8, 9]. Ketogenic diets may have antiepileptic properties as the utilization of ketone bodies in the brain instead of glucose delays or inhibits the degradation of γ-aminobutyric acid (GABA) transaminase and thereby enhances the

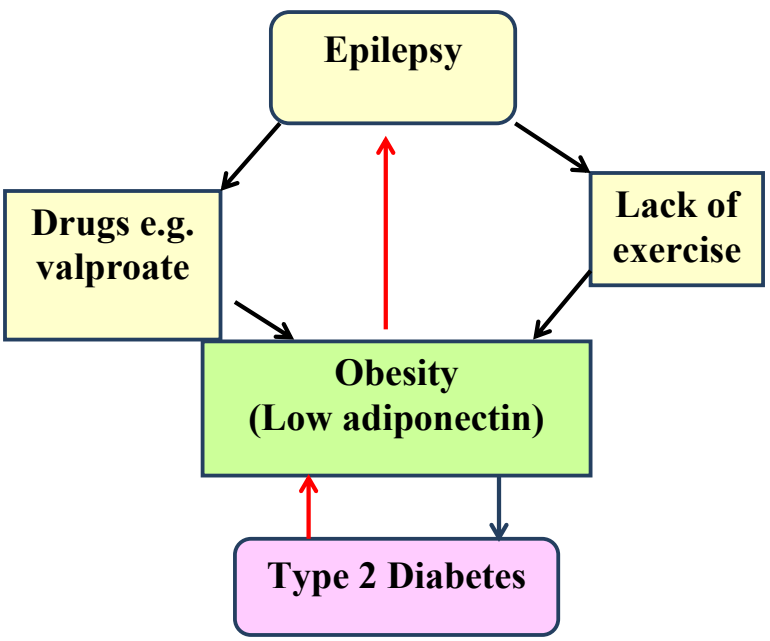

Figure 1. Inter-relationship between type 2 diabetes and epilepsy.

concentration of GABA [10]. In addition, it attenuates the levels of monoamines that enhance neuronal excitability, which explains the usefulness of the ketogenic diet in the management of resistant epilepsy [11]. The ketogenic diet can reduce or control seizures because it contains a high fat/low carbohydrate ratio, which causes overproduction of ketones in the liver and used by brain which is then metabolised in mitochondria to generate energy. However, the unfavorable effects of the ketogenic diet might carry risk to diabetic epilepsy patients.

The interactions between ketogenic diets and ASM favor synergism through their effects on the GABA receptor, transporter, and transaminase [12]. The inter-relationship between epilepsy, ketogenic-diet-induced acidosis, and ADDs is complex. Lactic acidosis is a rare adverse reaction to metformin, which has not interfered with the acidosis induced by the ketogenic diet [13]. Metformin is of value in controlling seizures by upregulating the activity of the AMP-activated protein kinase (AMPK) pathway and inhibiting the mammalian target of rapamycin (mTOR) [14]. In addition, metformin normalizes intracerebral GABA levels by modulating cerebral inflammation that is associated with epilepsy [15]. On the other hand, the use of some antiepileptic drugs is associated with the development of metabolic acidosis. One study reported that 71% of 80 patients who used topiramate had metabolic acidosis, which does not interact with using a ketogenic diet in the management of epilepsy [16, 17]. A ketogenic diet is a risk factor for the development of renal stones as a consequence of metabolic acidosis that is induced by topiramate or zonisamide [18]. The interaction between topiramate and ADDs is related to the pharmacokinetics of these drugs and not to the induction of acidosis. Topiramate reduces the systemic clearance of metformin and thereby elevates the serum level of metformin, which may cause unfavorable adverse reactions [19].

3. The Effects of Vagal Stimulation

Vagal nerve stimulation is an interventional approach used in the management of refractory epilepsy by implanting a device below the superior branch of the vagus nerve. Dysautonomia may develop when the device is implanted on the right side, as the branches of the right vagal nerve supply the atrial and ventricular sinusoids. Moreover, implantation of the device on the left side might also be associated with dysautonomia due to the overlapping of the branches of the vagus nerves on both sides. A noninvasive transcutaneous stimulator placed over the left vagal nerve produced electroencephalographic changes as a result of modulating the central neurotransmitters, including acetylcholine, GABA, serotonin, and noradrenaline [20]. A recent study reported no clinical or electrical evidence of cardiac arrhythmias in patients with refractory epilepsy treated with vagal nerve stimulation, and the patients responded normally to the sympathetic and parasympathetic activation tests [21].

It is important to mention that epilepsy patients are at risk of developing cardiac arrhythmias and impulse conduction defects due to seizures and ASM [22]. Cardiac arrhythmias are a result of intravenous administration of lacosamide in the treatment of status epilepticus, which can occur even at therapeutic doses [23]. Lacosamide-induced arrhythmias include prolongation of the PR period, atrioventricular defects, sinus node dysfunction, atrial tachycardia, and fatal arrhythmias [24-26]. Aging is an important risk factor for lacosamide-induced arrhythmias, as Runge *et al* demonstrated that patients who developed cardiac arrhythmias were aged > 65 years [27]. A significantly high plasma concentration of lamotrigine (> 14 mg/L) was associated with cardiotoxicity in two of 293 patients, while levetiracetam (> 80 mg/L) did not produce a cardiac effect in 106 patients [28]. Lamotrigine is a potential cardiotoxic drug; particularly in epilepsy patients who have cardiovascular diseases or who are treated with drugs acting on the cardiovascular system [29]. Phenytoin has dual effects on the heart, as it can cause bradycardia and hypotension as adverse reactions, and it can protect the heart from cardiac arrhythmias in heart failure [30, 31]. ASM have asymptomatic effects on the ventricular repolarization, as shown by the prolonged electrocardiographic parameters, including QTc, Tp-e, Tp-e/QTc after treatment with carbamazepine, sodium valproate, or levetiracetam [32]. Therefore, therapeutic drug monitoring for ASMs is recommended in epilepsy patients managed with vagal nerve stimulation to anticipate and/or avoid cardiac arrhythmias. Oral ADDs negatively affect the heart of epilepsy patients with T2D who are managed with vagal stimulation. Rosiglitazone and pioglitazone are cardiotoxic drugs that induce sudden death and ventricular arrhythmias by inhibiting

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ether-a-go-go-related potassium channels that are involved in the delay of ventricular repolarization [33]. Sulfonylureas have dual effects on the heart. They are proarrhythmogenic drugs due to their blocking effects on the extrapancreatic ATP-potassium channels [34, 35], and as a protective mechanism, these channels are opened in response to ischemia [36]. Subtle myocardial ischemia is reported in epilepsy; therefore, sulfonylureas may provide protective effects in epilepsy patients with T2D [37]. However, ASMs are of value in preventing seizure-induced cardiac arrhythmias, and they negatively affect the risk factors for cardiac arrhythmias including, T2D, dysautonomia, and obesity [38]. Experimental animal studies have shown that vagal nerve stimulation is of value in reducing the serum glucose level by enhancing the release of glucagon-like peptide (GLP)-1 [39]. Theoretically, vagal nerve stimulation as a part of the management of refractory epilepsy can also play a role in controlling the blood glucose level if the patients have concomitant T2D. Therefore, vagal stimulation is of value for both epilepsy and T2D, but it negatively impacts the patients treated with ASMs and/or ADDs, which participated in the cardiac arrhythmias or conduction defects.

4. Effects of Antiepileptic on Diabetes Mellitus

ASMs impact diabetes adversely through different mechanisms. Weight gain is a known adverse reaction to ASMs, which may be related to genetic predisposition factors [40]. Sodium valproate induces weight gain after 3 months that peaks after 6 months of treatment [41], and it is influenced by many factors, such as gender, age, body mass index before initiation of treatment, and type of epilepsy [42]. Sodium valproate produces hyperinsulinemia [43, 44], and hyperleptinemia, which may be the cause of weight gain [44, 45]. This effect may adversely affect patients with epilepsy and diabetes, as it may cause insulin resistance rather than reduce serum glucose levels [46]. In addition, sodium valproate inhibits glucose transporter (GLUT1) activity in the brain [47]. Moreover, sodium valproate therapy is associated with dyslipidemia in terms of high serum levels of total cholesterol and low-density lipoprotein, which adversely affect epilepsy–diabetes patients at risk of developing atherosclerosis [48]. It has been reported that sodium valproate reduced the mean levels of C-reactive protein and the estimated glomerular filtration rate by 55% in 50 patients with refractory epilepsy without producing a remarkable effect on glycosylated hemoglobin [49].

5. Effects of ADDs on Epilepsy

ADDs interact with epilepsy itself or with ASMs. Metformin is related to the biguanides and acts by sensitizing the tissue to insulin and providing a neuroprotective effect. Metformin plays a role in the regulation of glucose levels in the brain. It has been found that metformin prevents the synthesis of polyglucosan in experimental animal models of Lafora disease (a recessive progressive myoclonic epilepsy) [50]. It exerts an important effect on the function of glial cells as it reduces the proinflammatory markers by activation of the AMPK pathway, and thereby eliminates the neuroinflammation, which is a risk factor for provoking seizures [51-54]. In experimental animal models, the overactivation of the mTOR pathway is linked with seizures [14, 55], and it has been found that metformin inhibits upregulation of the mTOR pathway, which eventually results in reducing proinflammatory markers, and seizure control [56, 57]. In addition, metformin's positive effects on epileptic-diabetic animal models went beyond lowering blood sugar and reducing seizures to improve histopathology and restore normal GABA neurotransmitter levels [58, 59]. The antiapoptotic and antioxidant effects of metformin are also involved in the neuroprotective effect of metformin in epileptic–diabetic animal models [60-62]. Patients with GLUT1 deficiency syndrome are vulnerable to seizures; therefore, metformin plays a role in the upregulation of GLUT1 in astrocytes, leading to the prevention of seizures and/or reducing the number of seizures [63-67]. The mechanisms of action of metformin on seizures are shown in Figure 2. Metformin therapy interacts adversely with topiramate at a pharmacokinetic level. In a clinical trial carried out on healthy subjects, topiramate reduced the systemic clearance of metformin, and this effect seems to be gender-based because it is more pronounced in women than men [19]. Sitagliptin is one of the dipeptidyl dipeptidase-4 inhibitors, which have a positive impact on epilepsy in experimental animal models with pentylenetetrazole-induced seizures, by reducing reactive oxygen species (antioxidant effect), normalizing of GABA level, suppressing of neuroinflammation (autophagy), and reducing neu-

ronal damage (antiapoptotic effect) [68]. The other beneficial effect of sitagliptin is preventing the conversion of epilepsy to disease-associated microglia by suppressing neuroinflammation [69].

Pioglitazone is related to the thiazolidinediones, which act by activating the peroxisome proliferator-activated receptors in the nucleus. Experimentally, pioglitazone has an antiepileptic effect, which is related to activation of the nitric oxide generation pathway [70], and it interacts synergistically with the ketogenic diet in prolonging the latency period of seizure induction by inhalation of flurothyl gas [71]. GLP-1 receptor agonists, *e.g.*, exenatide and liraglutide, do not produce serious adverse reactions. Liraglutide is well tolerated and reduces body weight when combined with metformin in T2D patients. Therefore, it can counteract the weight gain induced by sodium valproate in epilepsy patients with T2D. Experimental animal studies demonstrated that liraglutide was effective in reducing spontaneous seizures and preventing cognitive impairment in an animal model of epilepsy [72]. Wen *et al* demonstrated that patients with temporal lobe epilepsy showed a decrease in GLP-1 receptor expression and levels in the cerebral cortex slices, suggesting that liraglutide has an antiepileptic effect [73]. Sodium-glucose cotransporter inhibitors, *e.g.*, canagliflozin, dapagliflozin, and empagliflozin, are also of benefit in the management of T2D with epilepsy as they reduce body weight, and there is no evidence of adverse effects on the central nervous system. Experimentally, dapagliflozin stabilizes neurons by reducing sodium transport across the membrane, as it significantly reduced the spike-wave percentage assessed by electroencephalogram and improved the behavior in rats with pentylenetetrazole-induced seizures [74].

6. The Pharmacological Actions of ADDs and ASM at the Cellular Levels

The generation of free radicals contributes to the development of T2D and epilepsy. Because several ASMs and ADDs have been demonstrated to have varied effects on autophagy or ferroptosis, we anticipate synergistic, additive, or antagonistic effects. The influence of ASM and ADDs on autophagy and ferroptosis in epilepsy and T2D is summarized in Figure 3.

6.1. Effects of ADDs and ASMs on autophagy

There is a close link between epilepsy and autophagy because the characteristic pathological changes in epilepsy, including changes in the structures and functions of the synapse, structural changes in the glia, abnormalities in the neural circuits, and an imbalance in the neuronal excitatory and inhibitory amino acids, are under the regulation of autophagy [75-78]. Autophagy in epilepsy induces changes in the ion channels, e.g., the GABAA receptor or glutamate receptor, leading to interferance in neuronal excitability [76]. There is evidence that the severity of epilepsy is linked to the hyperactivation of mTOR, which results from the loss of activity of mTOR inhibitor proteins [79-81].Therefore, drugs that target neural autophagy are of benefit in the management of epilepsy as they restore neural structures and functions.

Because autophagy is altered in epilepsy, drugs that stimulate autophagy by activating AMPK or blocking the mTOR signaling pathway may benefit a variety of epilepsy patients [82]. ADDs with an autophagy inducer and/or mTOR property can be beneficial for people with epilepsy and T2D. According to various studies, metformin's pharmacological actions are explained by the fact that it is a potent autophagy inducer. Metformin promotes autophagy by modulating signaling pathways such as AMPK, STAT, and SIRT [83]. Furthermore, metformin can also induce autophagy by regulating the sodium-hydrogen exchanger, which is implicated in the etiology of slow wave epilepsy [84]. These pharmacological actions of metformin are inadequate to demonstrate that the medicine has ASM capabilities because it also affects other signaling pathways that induce autophagy (Table 1) [85, 86].

Sulfonylureas also increase autophagy via a mechanism related to mTOR inhibition [85, 87]. Sulfonylureas are ineffective against epilepsy since their potential to promote autophagy has not been demonstrated in animal models of the illness. In reality, sulfonylureas can produce convulsions by disrupting the ATP-sensitive potassium channel or by lowering the efficacy of anticonvulsant medications that impact the inwardly rectifying potassium channels. (Kir 4.1) [88, 89]. Glitazones stimulate the peroxisome proliferator-activated receptor (PPAR), enhancing cellular sensitivity to insulin. This family of medicines induces autophagy by scavenging free radicals

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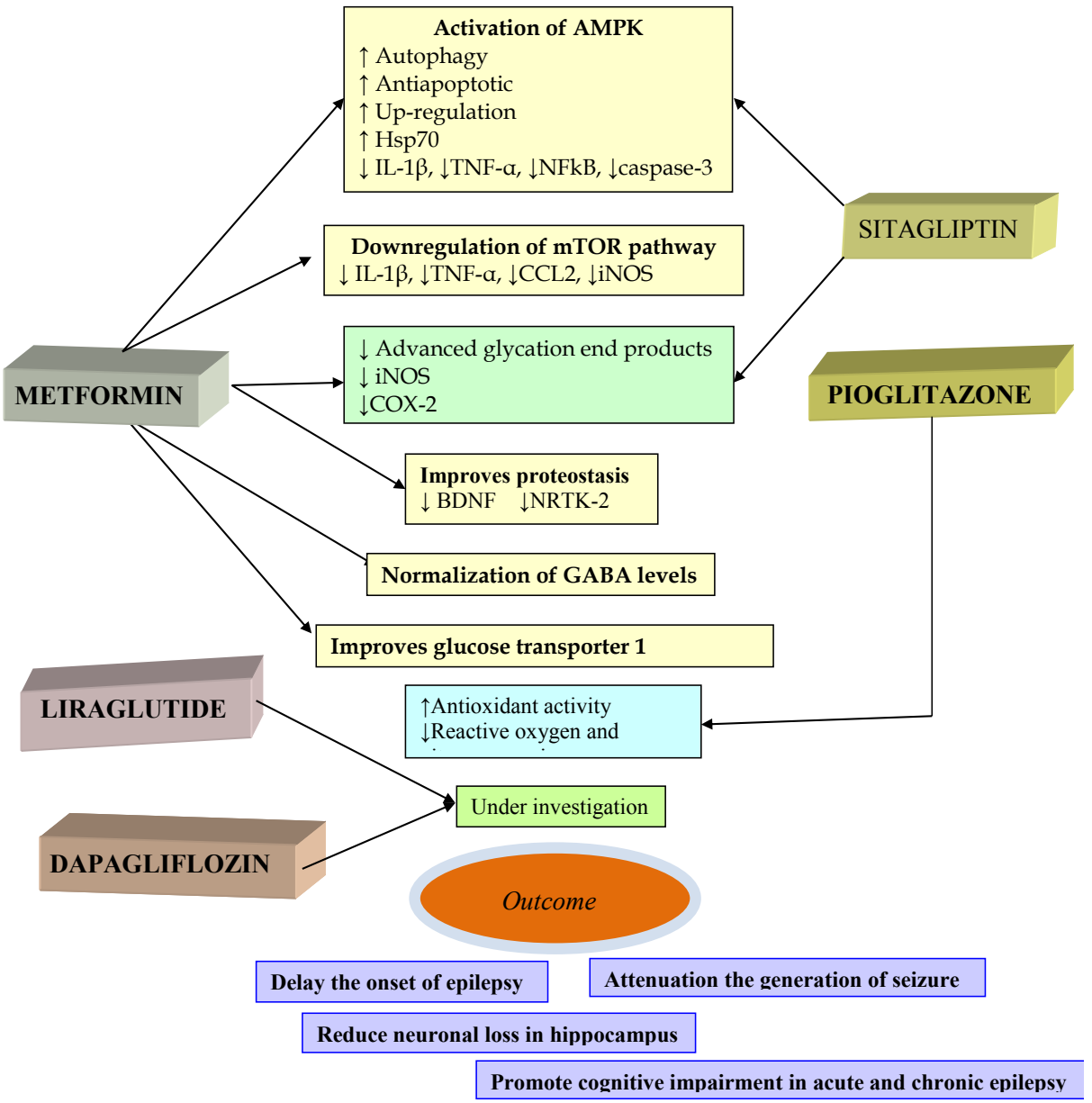

Figure 2. Mechanisms by which antidiabetic drugs improve the outcome of epilepsy.
Hsp70:heat shock protein 70, IL: interleukin, TNF: tumor necrosis factor, NFkB: Nuclear factor kappa B, CCL2: C-C motif ligand-2, iNOS: inducible nitric oxide synthetase, COX: cyclooxygenase, BDNF: brain derived neurotrophic factor, NRTK: non-receptor kinase, GABA: gamma-aminobutyric acid.

and activating antioxidant enzymes [90, 91]. Rosiglitazone inhibited the BDNF/TrkB pathway, which governs neural plasticity and produces seizures, in experimental studies, and had a favorable influence on people with T2D and epilepsy [92]. Rosiglitazone suppressed epileptiform discharges of hippocampal neurons in *in vitro* experimental models of epilepsy by limiting the release of presynaptic neurotransmitters and decreasing neuronal excitotoxicity caused by NMDA [93]. Dipeptidyl peptidase-4 (DPP-4) inhibitors lowered weight gain, metabolic dysregulation, and insulin resistance in obese mice by increasing autophagy activity and decreasing inflammation [94]. DPP-4 inhibitors enhance autophagosomes

Table 1. Signaling pathways that modulated autophagy by metformin.

Pathways	Action
ignaling pathways, including AMPK-related signaling pathways (e.g. AMPK/mTOR, AMPK/CEBPD, MiTF/TFE, AMPK/ULK1, and AMPK/miR-221), Redd1/mTOR, STAT, SIRT, Na^+/H^+ exchangers, MAPK/ERK, PK2/PKR/ AKT/ GSK3β, and TRIB3.	Activation
AMPK/NF-κB, Hedgehog, miR-570-3p, miR-142-3p, and MiR-3127-5p	Inhibition
PI3K/AKT/mTOR and endoplasmic reticulum stress	bidirectional

by a mechanism unrelated to the AMPK or mTOR signaling pathways [95]. DPP-4 inhibitors may thus be useful in the treatment of epilepsy. Sitagliptin decreases the severity of kainic acid-induced seizures in animals, and promotes the formation of disease-associated microglia (a kind of neuroprotective microglia) [69]. The drop in IL-1β, IL-6, and the enzyme-induced nitric oxide synthetase levels shows that sitagliptin's antiepileptic effects are caused by the blockage of the NF-kB signaling pathway and the control of inflammation [69]. Furthermore, sitagliptin improves the efficacy of pregabalin in preventing seizures caused by pentylenetetrazole via a variety of mechanisms, including lower glutamate levels, increased GABA levels, and autophagy-mediated neuroinflammation [68]. Dapagliflozin and canagliflozin are examples of sodium glucose cotransporter (SGLT2) inhibitors that induce autophagy via activating the AMPK/mTOR signaling pathways, as evidenced by a rise in the p-AMPK/AMPK ratio and a reduction in the p-mTOR/mTOR ratio [96, 97]. Dapagliflozin reduces the availability of glucose and the transfer of sodium across the neuronal membrane in animal models of pentylenetetrazole-induced seizures, decreasing the spike wave percentage observed on electroencephalograms [98]. The expression of the glucagon-like peptide-1 (GLP-1) receptor is linked to autophagy induction, implying that GLP-1 receptor agonists used to treat diabetes also activate autophagy [99]. Liraglutide has the potential to treat neurodegenerative diseases because it restores autophagy, which is impaired by endoplasmic reticulum stress (a neuronal damage mechanism) [100]. In lithium-pilocarpine animal models of status epilepticus, liraglutide reduces neuroinflammation (reducing IL-1β and TNF-α) and mitochondrial stress without lowering blood sugar [101]. In a nutshell, anti-diabetics benefit people with T2D and epilepsy by restoring autophagy, which is impaired by epilepsy and diabetes.

Autophagy dysregulation contributes to the pathogenesis of diabetes mellitus [102]. Mitophagy aids in the removal of toxic metabolites that cause mitochondrial damage and protects pancreatic β-cells from oxidative stress in T2D [103]. Some ASM impede autophagy function, which indicates that they are dangerous in diabetics. Sodium valproate has been shown in studies to have dual effects on autophagy. In a rat model of spinal cord injury, sodium valproate inhibited autophagy, providing neuroprotection by lowering neuronal death [104].

The mechanism by which sodium valproate causes autophagy is the inhibition of the mTOR signaling pathway [105]. In contrast, another study found that sodium valproate enhanced autophagy and cleared toxic compounds that caused neuronal damage [106]. Valproate may have some beneficial effects on diabetes because it protects the pancreatic β-cell by suppressing cellular apoptosis [107]. A separate study discovered that valproate lowers the effect of hyperglycemia on the activation of the coagulation and complement genes [105]. Valproate medication has been associated with large increases in body mass index and hyperinsulinemia in children with epilepsy [44], and another study found that valproate promotes dyslipidemia by dramatically boosting blood triglycerides and reducing high-density lipoprotein [108]. As a result, sodium valproate should not be used as an antiepileptic medication to treat people who have diabetes as well as epilepsy. Carbamazepine, an antiepileptic medication, is classified as an autophagy promoter. It stimulates autophagosomes by boosting the activity of AMPK-ULK1 [109]. It's fascinating to observe how carbamazepine protects against diabetes in mice by lowering the inflammatory response that causes insulitis and decreasing beta-cell activity [110]. There is little doubt that carbamazepine aids in the treatment of diabetic neuropathy because it stabilizes the neuronal cell membrane rather than inducing autophagy [111]. Unlike valproate, carba-

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mazepine does not cause dyslipidemia or weight gain [112]. Given that carbamazepine can cause polyuria and diabetic insipidus, it should be avoided in epileptic patients with diabetes. Pregabalin offeres neuroprotection by boosting autophagy and apoptosis and lowering the inflammatory response, according to literature studies [68]. Pregabalin, like carbamazepine, aids in the management of diabetic neuropathy by stabilizing the neuronal cell membrane [112]. Phenytoin restores autophagy activity by increasing the levels of autophagy-related proteins such as LC3II, p62, and Becline [113]. Gabapentin inhibited autophagy activity in experimental mice used to examine stroke caused by middle cerebral artery occlusion via increasing the phosphoinositide-3-kinase (PI3K)/protein kinase B (Akt)/mammalian target of rapamycin (mTOR) signaling pathway [114]. The β-secretase enzyme, which degrades the amyloid plaques, is likely to be the mechanism that stimulates autophagy in experimental mice with cognitive impairments [115]. Despite the lack of scientific or clinical proof that lamotrigine causes autophagy, it is used by diabetics in conjunction with anti-obesity medications to reduce body weight [116]. As a result, while establishing the therapeutic uses of antiepileptic drugs in patients with epilepsy and T2D, caution should be exercised.

6.2. Effects of ADDs and ASMs on ferroptosis

Dioxin et al. (2012) defined ferroptosis as a kind of controlled cell death characterized by the buildup of iron and reactive oxygen species [117]. Epilepsy, which is followed by ischemic stroke and trauma, has been connected to aberrant iron metabolism, which leads to the production of lipid peroxides and iron overload [118, 119]. Ferroptosis leads to pancreatic β-cell destruction, reduced glucose-induced insulin release, and impaired insulin synthesis in persons with type 2 diabetes due to an accumulation of iron and lipid peroxidation products in the mitochondria [120]. Metformin causes ferroptosis in malignant cells, which results in intracellular iron overload and lipid peroxidation products independent of the AMPK signaling pathway [121].

Metformin proved antiferroptosis in an experimental animal model of spinal cord injury by reducing malondialdehyde (MDA) levels and enhancing long-term results by blocking the inflammatory signaling pathway and activating the nuclear factor E2 signaling pathway [122]. The stimulation of the AMPK signaling pathway is likely to be the origin of this antiferroptotic activity, which was also seen *in vitro* [123]. As a result, metformin either increased or inhibited ferroptosis depending on the pathogenic circumstances. The ferroptosis process is initiated in epileptic adolescents treated with valproate or levetiracetam, as demonstrated by significantly higher blood levels of MDA and 8-OH-2-deoxyguanosine (a DNA damage marker) [124].

While phenytoin and carbamazepine have no effect on MDA levels [125-127], topiramate has been shown to up-regulate the lipid peroxidation process [125]. As a result, the involvement of ferroptosis in the pathophysiology of epilepsy-diabetes mellitus co-morbidities is currently being studied.

7. Conclusions

ADDs that reduce body weight are safe to prescribe for epilepsy patients with diabetes, and they show antiseizure effects by acting via different mechanisms and pathways. Drugs that activate autophagy or prevent ferroptosis are relatively safe for patients with epilepsy and diabetes. Further clinical studies are recommended to confirm the experimental evidence that showed that some ADDs delay the onset, prevent the generation of seizures, and improve cognitive function.

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Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Statement of Contribution of Researchers

Concept –M. Al-N.; Design – M. Al-N.; Supervision – M. Al-N.; Data collection – M. Al-N., S. Al-Z.; Data interpretation – M. Al-N.; Literature Search - M. Al-N., S. Al-Z.; Writing – M. Al-N.; Critical Reviews — M. Al-N., S. Al-Z.

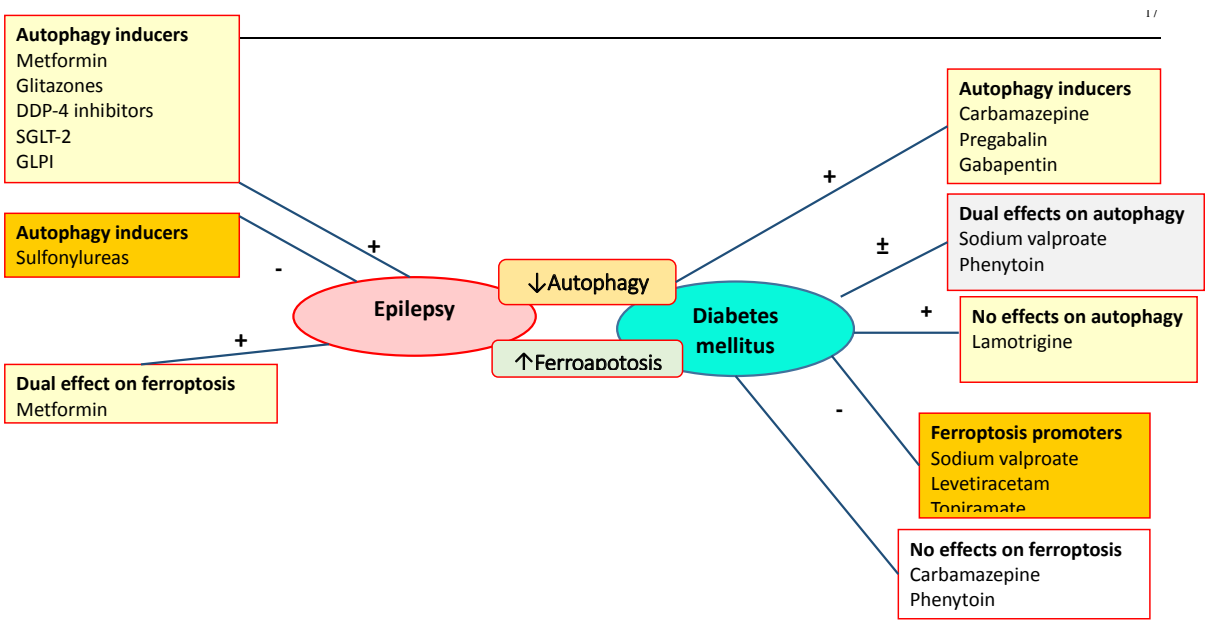

Figure 3. Schematic diagram showed the impact of antiepileptiics and antidiabetics on the autophagy and ferroptosis. (+): positive impact, (-): negative impact, DDP-4: Dipeptidyl peptidase, SGLT: sodium glucose cotransporter-2, GLP: Glucagon-like peptide

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