



Review article

Envisioning the neuroprotective effect of Metformin in experimental epilepsy: A portrait of molecular crosstalk



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ABSTRACT

Epilepsy is a neurological disorder characterized by an enduring predisposition to generate and aggravate epileptic seizures affecting around 1% of global population making it a serious health concern. Despite the recent advances in epilepsy research, no disease-modifying treatment able to terminate epileptogenesis have been reported yet reflecting the complexity in understanding the disease pathogenesis. To overcome the current treatment gap against epilepsy, one effective approach is to explore anti-epileptic effects from a drug that are approved to treat non-epileptic diseases. In this regard, Metformin emerged as an ideal candidate which is a first line treatment option for type 2 diabetes mellitus (T2DM), has conferred neuroprotection in several in vivo neurological disorders such as Alzheimer's diseases (AD), Parkinson's disease (PD), Stroke, Huntington's diseases (HD) including epilepsy. In addition, Metformin has ameliorated cognitive alteration, learning and memory induced by epilepsy as well as in animal model of AD. Herein, we review the promising findings demonstrated upon Metformin treatment against animal model of epilepsy however, the precise underlying mechanism of anti-epileptic potential of Metformin is not well understood. However, there is a growing understanding that Metformin demonstrates its anti-epileptic effect mainly via ameliorating brain oxidative damage, activation of AMPK, inhibition of mTOR pathway, downregulation of α -synuclein, reducing apoptosis, downregulation of BDNF and TrkB level. These reflects that Metformin being non-anti-epileptic drug (AED) has a potential to ameliorate the cellular pathways that were impaired in epilepsy reflecting its therapeutical potential against epileptic seizure that might plausibly overcome the limitations of today epilepsy treatment.

1. Introduction

Epilepsy is a serious neurological condition characterized by disrupted brain activity and rapid occurrence of epileptic seizure due to abnormal or excessive brain neuronal activity. More precisely, epilepsy is caused due to aberrant synchronized neuronal firing arising due to imbalance between excitatory and inhibitory neurotransmission [1]. Epilepsy has emerged has a serious global health concern affecting around 70 million people, whereby epilepsy barely stand-alone and the condition is more worsened by the associated conditions known as

comorbidities [2]. It is well established that people with epilepsy (PWE) have a high chance of developing cognitive dysfunction, depression, anxiety, schizophrenia, autism [3,4] as well as Alzheimer's diseases (AD) [5–7] sharing a bi-directional relationship.

Epilepsy can be categorized into genetic or idiopathic on the ground of presumed underlying causes. Epilepsy is due to a genetic predisposition of the brain to initiate seizures, whereby acquired epilepsy is originated from a known lesion or acute insult that initiates a series of cellular, molecular and physiological disruption giving rise to seizures [1]. Though epileptogenesis and epileptic seizures have been well

Abbreviations: PWE, people with epilepsy; TLE, temporal lobe epilepsy; SE, status epilepticus; PME, progressive myoclonus epilepsy; T2DM, type 2 diabetes mellitus; AED, anti-epileptic drug; LD, Lafora disease; AD, Alzheimer's diseases; HD, Huntington's diseases; PD, Parkinson's disease; PTZ, pentylentetrazol; KA, Kainic acid; AMPK, 5'-adenosine mono-phosphate-activated protein kinase; mTOR, mammalian target of rapamycin; BDNF, brain derived neurotrophic factor; TrkB, tyrosine receptor kinase B; PI3K, phosphatidylinositol 3 kinase; ROS, reactive oxygen species; SLE, seizure-like events; KO, knockout; ETC, electron transport chain; MDA, Malondialdehyde; GSH, reduced glutathione; SOD, superoxide dismutase; MWM, Morris water maze; NOR, novel object recognition

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studied since very long time, the underlying pathomechanism of epileptogenesis is still elusive [8]. Nevertheless, there is an increased understanding about the pathogenic role of mutation [9], oxidative stress [10,11], brain injury [12,13] in epilepsy. However, the contribution of brain inflammation in the pathogenesis of epilepsy [14–18] is widely acknowledged. This is evidenced by the fact that anti-inflammatory drugs have demonstrated promising disease-modifying outcomes in an experimental model of epilepsy [16,19,20].

Moreover, the currently available anti-epileptic drugs (AEDs) which act via voltage-gated Na⁺ channels, K⁺ channels, T-type Ca²⁺ channels and inhibit neuronal excitability [21] only provides symptomatic treatment without altering the disease progression. In addition, 1/3rd of the patients are not treated with mainstream AEDs [22] and the AEDs are itself causing cognitive dysfunction [23–25] in addition to minimizing seizure. This reflects the burning needs of exploring disease-modifying anti-epileptogenic therapy that could overcome the current treatment gap in epilepsy. One strategy that has gained attention in recent days is to explore novel anti-epileptic effects among drugs that are commonly used in the treatment of other diseases [26]. This strategy has identified several novel AEDs (Metformin, Rapamycin, Everolimus, Losartan, Celecoxib, Bumetanide, Amiloride, Dipeptidyl peptidase-4 inhibitors) [26–28] from already used drugs used to treat non-epileptic disorders. Herein, the topic of the interest is Metformin, which has gained increased attention due to its promising neuroprotective effects in plethora of neurological disorders including Parkinson's diseases (PD) [29], AD [30], Schizophrenia [31], Stroke [32], Huntington's diseases (HD) [33].

Metformin is a dimethylbiguanide, derivative of guanidine, isolated in the 1920s [34] and a first line drug for the treatment of type 2 diabetes mellitus (T2DM) [35,36]. However, ample amount of pre-clinical experiments has reported the promising therapeutic effect of Metformin against experimental epilepsy [37,38] and in Lafora disease (LD) [39,40].

Plethora of studies has reported the association of epilepsy with DM, which is mainly based on studies from T1DM [41,42]. However, a population based study from Taiwan reported that people with T2DM are at 1.5 times higher risk of developing epilepsy than matched controls [43]. The precise underlying mechanism relating DM and epilepsy is not well understood, however we can speculate blood-brain barrier (BBB) breakdown in DM might play a role in epileptogenesis. As increased BBB permeability might lead to the invasion of pro-inflammatory cytokines into the brain [44]. Inflammation occurs in the CNS due to leaky BBB which can further initiate epileptogenesis as well as induction of epileptic seizures [45]. This is supported by the findings reporting BBB breakdown during DM [46] and BBB dysfunction causing epileptic seizure [47–49]. Furthermore, BBB disruption has been widely implicated in post-traumatic epilepsy (PTE) [50], AD [51] and in cognitive and psychiatric complications of T2DM [52]. All these reflect that Metformin which has been reported to attenuate BBB disruption [53] might be effective in treating diabetes patients which are at risk of developing epilepsy.

Metformin exhibited a potential to ameliorate symptoms of epileptic seizure in addition to its potential role to modulate the molecular and cellular changes including oxidative stress, neuroinflammation, apoptosis, and neuronal loss observed during the initiation and progression of the disease [54]. These findings strongly implicate that Metformin stands uniquely as a possible therapeutic alternative against epileptic seizures that deserves further exploration. On the ground of available pre-clinical current review discusses the therapeutic role of Metformin against epileptic seizures as well as elaborate its putative underlying molecular mechanisms of its action.

2. Metformin treatment delayed seizure onset, reduced seizure frequency and duration as well as terminates seizure: update from experimental findings

Anti-epileptic effect of Metformin has been reported in wide ranges of experimental epilepsy as discussed below. In a pentylenetetrazol (PTZ) kindling epilepsy model in mice (37 mg/kg, intraperitoneal (I.P.) alternate day for 28 days), Metformin (200 mg/kg, I.P.) administration on alternate day of PTZ injection significantly suppressed the progression of kindling. The anti-epileptic effect of Metformin is evidenced by the significant decrease in seizure score from the 8th to the 14th PTZ administration ($p < 0.05$ from the 8th injection to the 11th injection and $p < 0.01$ from the 12th injection to the 14th injection) [55]. In a similar line of investigation, Metformin treatment (200 mg/kg, I.P. for 2 weeks) ameliorated PTZ-induced seizures (50 mg/kg, I.P., alternate days for 2 weeks), demonstrated increased seizure onset latency and decreased seizure duration [37]. Similarly, in a PTZ (70 mg/kg I.P.) induced acute seizure model and Kainic acid (KA) (1.0 nmol in 50 nl saline, injected in hippocampus) induced chronic seizure, chronic Metformin treatment (2 mg/ml, 30 days) facilitate the acute seizure termination, decrease the mortality in PTZ-induced acute seizures, shortened the duration of epileptic activity and duration of seizure-like events (SLEs) in chronic seizures [56]. In a rat model of Pilocarpine (360 mg/kg, I.P.) induced status epilepticus (SE), Metformin (250 mg/kg, I.P. for 5 days) administration after 45 days of SE induction demonstrated reduction in the progression of seizures reflecting its anti-convulsant and anti-epileptic potential [28]. In a zebrafish larvae model of PTZ-induced seizure (5 mmol/L), Metformin pre-treatment (2 μmol/L) did not significantly affect their total movement but minimize their seizure-type movement by around 28%. However, swimming pattern do not exactly confirm the suppression of seizure as electrophysiological recording does [57]. All these findings reflect towards an anti-epileptic potential of Metformin against PTZ, KA and Pilocarpine induced epilepsy model however, clinical findings are yet to be registered.

3. Metformin against LD

LD is a fatal form of progressive myoclonus epilepsy (PME) [58] with a prevalence of < 4 patients per 1,000,000 populations [59]. Mutations in the gene encoding either the glycogen phosphatase laforin or the E3 ubiquitin ligase malin causes LD [60] with no therapy available till date. However, in 2016, European Medicines Agency (EMA) granted orphan designation to Metformin for the treatment of LD [39]. Hence, Metformin has been extensively studied against animal model of LD.

In a PTZ-induced seizure (50 mg/kg, single I.P. injection) in a malin knockout (KO) model of LD, Metformin (3 mM) reduces PTZ-induced seizures, mortality, and seizure duration, ameliorating the hyperexcitability detected in mice lacking the malin protein [40]. In a case report of 12 genetically confirmed LD patients treated with titrated dose of Metformin (mean maintenance dose 1167 mg/kg/day), demonstrates clinical responses in 3 patients but no clinical benefits were reported in 9 patients. It was hypothesized that the poor clinical outcome might be due to the relatively advanced stage of disease in small cohort hence, cannot exclude a role of Metformin in slowing down LD progression [39]. However, Metformin was well tolerated in all patients without any adverse effects.

Though there is low amount of evidences supporting the neuroprotective role of Metformin against LD, Metformin is worth to explore extensive against experimental LD model as well as in large cohort of patients.

4. Metformin ameliorated the brain oxidative stress in epilepsy

Oxidative stress has been widely acknowledged in the initiation and progression of epileptic seizures [10,61,62]. Neuronal hyperexcitability

and oxidative injury generated by an excessive production of free radicals might contribute in the initiation and progression of epilepsy [10]. Recent review has discussed the role of oxidative stress in SE and suggest oxidative stress as a marker of SE [63]. However, there is a contradicting view about either oxidative stress is a cause or a consequence of epilepsy; as the prolonged seizure-related neuronal excitation results in increased reactive oxygen species (ROS) production, due to unpaired electrons escaping the electron transport chain (ETC) and reacting with molecular oxygen, thus generating superoxide, which might contribute to seizure-induced brain damage [64]. In recent days, several anti-oxidants has demonstrated their anti-epileptic effect in experimental studies mainly via protection against oxidative damage [65,66]. Metformin has also demonstrated its ameliorative effect against epilepsy induced oxidative damage in experimental studies as discussed below.

Metformin (200 mg/kg, I.P.) treatment has demonstrated protective effect against oxidative damage induced by PTZ-kindling, which is evident by decrease in the level of Malondialdehyde (MDA) ($p < 0.05$) and upregulation of reduced glutathione (GSH) ($p < 0.05$) as compared to PTZ treated group. This speculate that anti-epileptic effect of Metformin is at least partly mediated via its anti-oxidant property [55]. In a similar line of study, Metformin (200 mg/kg, I.P.) treatment ameliorate the brain level of MDA, GSH and Catalase (CAT) activity induced by PTZ. Metformin treated group showed significant reduction in MDA ($p < 0.01$) and significant increase ($p < 0.01$) in GSH concentration as compared to PTZ group whereas no significant increase was obtained in CAT activity compared to PTZ-treated group [37]. This finding provide compelling evidence reflecting the plausible role for oxidative stress in pathophysiology of PTZ-induced seizure and suggest that the anti-epileptic effect of Metformin is related to its anti-oxidant properties [37].

5. Effects of Metformin on adenosine monophosphate-activated protein kinase (AMPK) activation and inhibition of mammalian target of rapamycin (mTOR) pathway in epilepsy

AMPK is an important metabolic sensor in the brain [67]. When AMPK is activated, it phosphorylates tuberlin and raptor (mTOR cascade proteins), resulting in a rapid suppression of the mTOR pathway activity [68], hence an effective way to regulate mTOR pathway function is through activation of AMPK. Decreased level of AMPK has been observed in an epileptic brain [56]. Hence, activation of AMPK has been a plausible mechanism required to alleviate epileptic seizure. Metformin is a well-known activator of AMPK [69].

Immunofluorescence labeling of the epileptic mice (hippocampus and cortex) found AMPK expression in the neurons, but not in astrocyte. Moreover, AMPK protein level was significantly downregulated in Temporal lobe epilepsy (TLE) patients as compared with the control [56]. In acute seizure model, treatment with Metformin significantly increased p-AMPK level whereas chronic Metformin treatment does not regulate AMPK level, but significantly increased the level of p-AMPK. This finding suggests the potential of Metformin on the activation of AMPK in experimental epilepsy [56]. In an experimental LD model (malin KO, *Epm2b*^{-/-}), Metformin (12 mM, dissolved in water) treated group demonstrated an enhanced activation of AMPK in both control and KO malin mice as evidenced by upregulated levels of the phosphorylated form of the catalytic subunit of the AMPK complex (pThr172- AMPK α) [70].

The role of mTOR pathway in epilepsy is well established. Hyperactivated mTOR have been implicated in the pathogenesis of several animal models of acquired epilepsy, such as infantile spasms (IS), TLE, SE and absence epilepsy [71,72]. Moreover, mTOR inhibition has emerged as a promising therapeutic target against epilepsy [71,73]. In an experimental model of TLE, Metformin has activated AMPK, inhibited mTOR pathway function and demonstrates beneficial anti-epileptic effects [38]. Metformin treatment significantly elevated AMPK

phosphorylation in the neocortex as well as reduced Protein kinase B (PKB) phosphorylation in the neocortex and hippocampus [38]. In the immunohistochemical analysis of coronal sections of the hippocampus labelled with a monoclonal antibody specific to p-AMPK and p-mTOR, p-AMPK double staining shows decreased immunoreactivity whereas p-mTOR double-staining shows increased immunoreactivity after Pilocarpine treatment compared to the control [28]. Whereby, Metformin treatment (250 mg/kg/day) increased the protein expression of p-AMPK and decreased the protein expression of p-mTOR as compared to Pilocarpine treated group [28]. This finding supports the notions that anti-epileptic effects of Metformin is partially mediated by its potential to inhibit mTOR pathway and activate AMPK.

6. Other proposed mechanism of Metformin protective effects in experimental epilepsy

In addition to the above-discussed mechanism, there are several others plausible mechanism via which Metformin has conferred its neuroprotection against experimental epilepsy.

Alpha-synuclein (α -synuclein) is a small, acidic synaptic protein composed of residues of 140 amino acid normally soluble and is abundantly localized in the neuronal synaptic terminals of the brain [74]. Earlier findings has reported an up regulation of α -synuclein in different neurological disorders including epilepsy [75,76] and PD [77]. Metformin treatment caused significant attenuation in α -synuclein upregulated in the hippocampal CA3 region induced by PTZ treatment [37]. This study suggest that anti-epileptic effect of Metformin might be plausibly due to downregulation of α -synuclein.

Apoptotic neuronal cell death is involved in pathogenesis of epileptic seizures involving activation of key enzymes such as caspase-3 that ends with cell death. Apoptosis induction in brain and increased of caspase-3 has been observed in epileptic brain [78–80]. Metformin treatment has been reported to decrease apoptotic protein (caspase-3) and downregulated the signal of cleaved caspase-3 products induced by PTZ administration [37]. The PTZ-treated group showed a significant increase in apoptotic protein (caspase-3) expression in hippocampal regions compared with the normal group ($p < 0.01$), while the Metformin treated group showed a significant decrease in caspase-3 compared with the PTZ groups ($p < 0.01$). Moreover, the PTZ group showed a strong signal of cleaved caspase-3 products, which in turn was downregulated in the Metformin treated group. Metformin treated group showed a significant decrease in β -catenin which was initially expressed in hippocampal regions of the PTZ group [37]. Metformin treatment (20 mM) has exerted its potential to prevent apoptotic neuronal death induced by PTZ in cultured human cortical (HCN-2 cell) neurons [81]. Moreover, treatment with Metformin (200 mg/kg) reduced apoptosis in an in vivo PTZ-induced SE model probably by ameliorating the C/EBP homologous protein (CHOP) expression and suppressing endoplasmic reticulum (ER) stress through the AMPK-phosphatidylinositol 3 kinase (PI3K)-c-Jun NH2 pathway [82]. All these finding demonstrates the anti-apoptotic role of Metformin against epileptic seizure. Brain-derived neurotrophic factor (BDNF) and its receptor Tropomyosin receptor kinase B (TrkB) signaling has been reported to promote epileptogenesis in an experimental model of mesial TLE [83]. Increased expression of BDNF and TrkB has been reported in an epileptic brain [84,85]. This suggest that downregulation of BDNF and TrkB level might lead to an anti-epileptic potential. Metformin treatment (250 mg/kg, I.P.) significantly downregulated the expression levels of BDNF and TrkB which was earlier increased due to Pilocarpine administration [28]. The anti-epileptic effect demonstrated by Metformin in this study might be plausibly due to its BDNF and TrkB lowering potential.

7. Ameliorative effect of Metformin in cognition, learning and memory

Cognition function is the most common and severe comorbidity of epilepsy and is impaired in PWE compared to the general population [86]. Different ranges of data (50% and 50–70%) [87,88] reported the prevalence of cognitive impairment in PWE. PWE demonstrates cognitive disruption mainly in one or more domain including learning, memory, attention deficits, executive function, language dysfunction with memory impairment being the most prevalent [89–93]. Moreover, large number of evidences supports the notion that epilepsy and AD are interconnected [7] and PWE commonly exhibit cognitive impairment similar to AD patients, which in turn are at a greater risk of developing epilepsy compared to age-matched controls [94]. More precisely, seizures have been reported in 28% of AD cases which might be due to late manifestation of the disease process during the progression of neurodegeneration [95]. Cognitive impairment has been a common pathogenic denominator in epilepsy and AD [96,97]. A seizure might contribute to the progressive cognitive decline and neurodegeneration in AD [96]. However, either seizure directly contribute to the progressive pathology or memory impairment in AD remains greatly unknown. This alarming data reflects the need of exploring novel anti-epileptic drugs that not only minimizes the seizures but also ameliorates the related cognitive impairment, which could help in untangling the complex relationship between epilepsy and AD as well. Metformin has been emerged as an ideal therapeutic candidate that has ameliorated cognitive impairments in an experimental model of epilepsy and AD as discussed herein.

In a PTZ-induced cognitive impairment, Metformin (200 mg/kg, I.P.) ameliorated the cognitive impairment assessed in the Morris water maze (MWM) test. PTZ kindled mice demonstrated significantly prolonged escape latency compared to the control group ($p < 0.01$). However, the poor performance was ameliorated by pre-treatment with Metformin ($p < 0.01$). PTZ kindled mice spend less time in the target quadrant in comparison to control group ($p < 0.01$), while Metformin pre-treatment significantly improved the performance ($p < 0.01$). Moreover, number of crossing the platform in PTZ-kindling group was lowered as compared to the control group ($p < 0.01$), which in turn was increased with Metformin pre-treatment ($p < 0.01$) [55]. This experimental finding provides the compelling proof-of-concept that Metformin treatment ameliorates the epilepsy induced cognitive impairment.

In an experimental investigation of scopolamine (1 mg/kg, I.P.) induced learning and memory deficits resembling AD like pathology, Metformin treatment has alleviated learning and memory deficits as evidenced by MWM test and modified elevated plus-maze (MEPM) test [98]. Regarding the underlying mechanism of Metformin against scopolamine induced disruption in spatial memory; authors conclude that Metformin effect is not due to its effect on acetylcholine in the hippocampus but it might be due to its capacity to improve CREB and p-AMPK levels reduced by scopolamine as well as its potential to reverse the effect of scopolamine on MDA, total antioxidant status (TAS), and SOD levels in the hippocampus [98]. In a similar line of investigation, Metformin treatment dose-dependently improved scopolamine-induced (1 mg/kg, I.P.) cognitive alteration as evidenced by MWM and passive avoidance task. In addition Metformin ameliorated the scopolamine induced increased brain oxidative stress, inflammation, total Akt, with reduction in its active phosphorylated form, and elevated phosphorylated Tau [99]. However, surprisingly Metformin treatment did not demonstrated any alteration in acetyl cholinesterase specific activity [99] which role has been widely acknowledged in learning and memory. These findings clearly implicate that Metformin has an ability to prevent the development of dementia related with AD.

In an experimental animal model of AD using *APP/PS1* double transgenic mice, Metformin (200 mg/kg, I.P.) treatment rescues spatial memory deficits, prevents neuronal cell death, increases adult

hippocampal neurogenesis [30] as spatial and temporal deficits in AD is correlated with neuronal loss in the hippocampus and cortex [100]. The escape latency in Metformin-treated *APP/PS1* mice was lowered significantly as compared to the saline-treated *APP/PS1* mice. As well as Metformin, treatment ameliorated the spatial memory formation of *APP/PS1* mice as evidenced by the fact that Metformin-treated *APP/PS1* mice demonstrated increased time spent in the target quadrant and more crossovers as compared to *APP/PS1* control [30]. Similarly, in the SAMP8 mouse model of AD, Metformin treated group (20 mg/kg or 200 mg/kg, subcutaneous injections) improved acquisition and retention in T-maze and novel object recognition (NOR) test as Metformin treated group took significantly fewer trials to reach their first avoidance as compared to normal control mice [101]. The underlying mechanism relating the protective effect of Metformin in learning and memory has been correlated with decreased phosphorylated Tau by Metformin treatment [101] as decrease in phosphorylated Tau has been reported to improve memory in mouse models of AD. These finding reflects that Metformin might be an alternate therapeutic option for the treatment and prevention of memory impairment either in epilepsy or in AD.

8. Discussion

Epilepsy is a devastating neurological condition affecting around 1% of global population [102] with alteration in neuronal activity at molecular, cellular, and circuit levels. Despite the better understanding of the epilepsies mechanism in recent days, the mainstream AEDs acting via several targets are not able to completely terminate the disease-mechanism ending up with challenges of drug resistance and side effects limiting the pharmacological treatment of epilepsy [103]. This reflect the burning need of exploring novel treatment strategies against epilepsy that not only terminate the disease progression but also minimize the epilepsy related comorbidities.

Developing a novel anti-epileptic therapy is a time-consuming process with stringent regulatory compliance, in addition to huge investments and tremendous scientific efforts. To overcome this, an alternate strategy is to explore novel anti-epileptic compound from a drug that are already FDA approved and have been extensively used in human, which has ability to target the pathways, and cellular process that were altered in epilepsy. Metformin stand as an ideal candidate in this regard, which is a not-AED and has demonstrated its anti-epileptic property in a range of experimental model of epilepsy as evidenced by delay onset of seizure, reduced seizure frequency and duration, seizure termination and behavioral improvements [28,38,55,56].

Metformin was originally used for the treatment of T2DM however, in recent days there is a growing interest in exploring the therapeutic potential of Metformin against several neurological disorders where Metformin treatment has demonstrated promising results [31,34,104,105]. Though the precise underlying mechanism about the anti-epileptic potential of Metformin is not well identified, however there is a growing understanding that Metformin demonstrates its anti-epileptic effect mainly via ameliorating brain oxidative damage, activation of AMPK, inhibition of mTOR pathway, downregulation of α -synuclein, reducing apoptosis, downregulation of BDNF and TrkB level [28,37,38,55,56] (Fig. 1). Despite the fact that role of inflammation has been acknowledged in epilepsy [15,18,106] and Metformin has exhibited anti-inflammatory effects [107,108], it is surprising that Metformin potential to modulate the inflammatory markers which are highly expressed in epilepsy is not explored in an experimental studies discussed herein. The anti-epileptic potential of Metformin has been only evaluated against PTZ, KA and Pilocarpine induced model of epilepsy. Evaluating the therapeutical potential of Metformin against diverse ranges of pro-convulsant in animal model resembling different clinical phenotypes will confirm and validate the anti-epileptic potential of Metformin. However, despite the ample amount of experimental evidences, the clinical findings regarding anti-epileptic potential of

Protective effect of Metformin treatment in Epilepsy

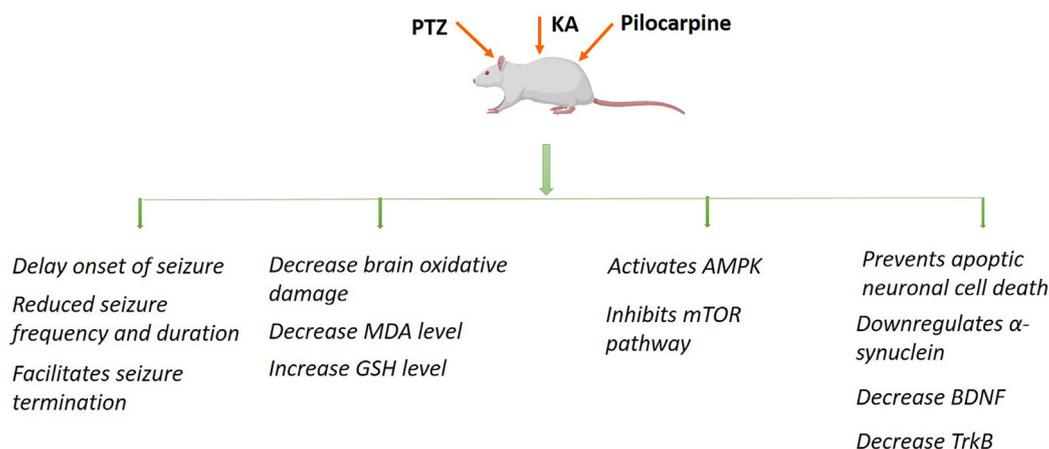


Fig. 1. Protective effect of Metformin treatment in epilepsy.

Metformin treatment has exerted neuroprotective role in diverse ranges of neurological disorders. Metformin has been extensively evaluated for its therapeutic role against several experimental model of epilepsy including Lafora diseases where Metformin treatment has delayed seizure onset, reduced seizure duration and frequency as well as facilitates seizure termination. However, the underlying mechanism of Metformin anti-epileptic effect is not well understood but Metformin anti-epileptic effect might be plausibly mediated through its potential to ameliorate brain oxidative damage, to activate AMPK and inhibit mTOR, reduced apoptic neuronal cell death, downregulation of α -synuclein, BDNF and TrkB. This speculation is based on the fact that all these has been contributing in the pathogenesis of epilepsy. PTZ, Pentylene tetrazol; KA, Kainic acid; AMPK, 5'-adenosine mono-phosphate-activated protein kinase; mTOR, Mammalian target of rapamycin; BDNF, Brain derived neurotrophic factor; TrkB, Tyrosine receptor kinase B; MDA, Malondialdehyde; GSH, Reduced glutathione.

Metformin is yet to be reported except in a single clinical case of LD [39].

Metformin has been effective against ameliorating cognitive impairment [30,98] as well including epilepsy induced cognitive impairment as well [55] (Fig. 2). This strongly raises the possibility that Metformin might be an ideal candidate that could help in untangling the complex association between epilepsy and AD via ameliorating cognitive impairment as AD is associated with cognitive decline and increased risk of seizure incidences whereby cognitive impairment is among the shared phenomena in both the diseases [96,97].

Metformin has been reported to rapidly cross BBB distributed to several brain regions [109,110] and exerts neuroprotection [111]. Metformin with its multifaceted properties, safety and pharmacokinetic profile, is a promising candidate against epilepsy [57]. To conclude, we suggest that Metformin due to its neuroprotective potential might be an excellent therapeutic option against epilepsy, which might ultimately open the window of opportunities in exploring novel therapeutic avenues not only against epilepsy as well as in cognitive decline. However, further research is warranted for the clinical translation of Metformin against epilepsy.

Ameliorative effect of Metformin in Cognitive function

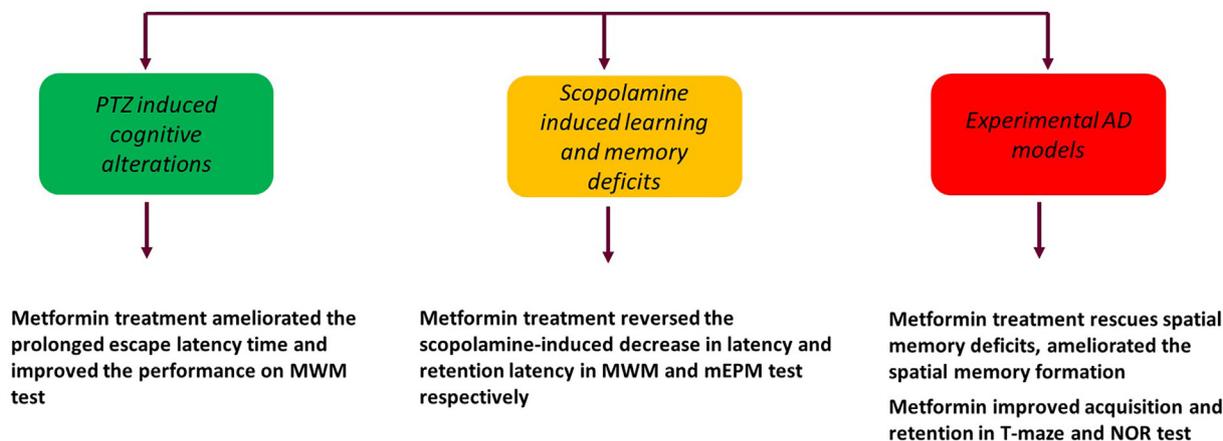


Fig. 2. Ameliorative effect of Metformin in cognitive function.

Metformin has demonstrated its ameliorative potential on cognitive impairment caused by PTZ, Scopolamine and even in an experimental AD models. Plausible mechanism of protective effect of Metformin on PTZ-induced cognitive deficits might be due to the ameliorative potential of Metformin on brain oxidative stress and activation of AMPK [55]. Ameliorative effect of Metformin on Scopolamine induced learning and memory deficits might be due to Metformin effect on acetylcholine, CREB, p-AMPK as well as on oxidative stress [98]. However, the underlying mechanism of Metformin ameliorative effect on cognitive deficits in experimental AD model has been correlated with reduction of APP-C99 and phosphorylated Tau [112]. PTZ, Pentylene tetrazol; AMPK, 5'-adenosine mono-phosphate-activated protein kinase; AD, Alzheimer's diseases; APP, Amyloid precursor protein; MWM, Morris water maze, mEPM, Modified elevated plus maze; NOR, Novel object recognition.

Author's contribution

NHS conceived, carried out the literature review and drafted the manuscript. YNP and KKL provided critical inputs, revised and edited the final version of the manuscript. All authors read and approved the final manuscript.

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Declaration of Competing Interest

The authors declare that there is no conflict of interest regarding this work.

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Ethics approval and consent to participate

Not applicable.

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