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Role of the mTOR signaling pathway in epilepsy

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ABSTRACT

Epilepsy, a common neurological disorder and cause of significant morbidity and mortality, places an enormous burden on the individual and society. Presently, most drugs for epilepsy primarily suppress seizures as symptomatic therapies but do not possess actual antiepileptogenic or disease-modifying properties. The mTOR (mammalian target of rapamycin) signaling pathway is involved in major multiple cellular functions, including protein synthesis, cell growth and proliferation and synaptic plasticity, which may influence neuronal excitability and be responsible for epileptogenesis. Intriguing findings of the frequent hyperactivation of mTOR signaling in epilepsy make it a potential mechanism in the pathogenesis as well as an attractive target for the therapeutic intervention, and have driven the significant ongoing efforts to pharmacologically target this pathway. This review explores the relevance of the mTOR pathway to epileptogenesis and its potential as a therapeutic target in epilepsy treatment by presenting the current results on mTOR inhibitors, in particular, rapamycin, in animal models of diverse types of epilepsy. Limited clinical studies in human epilepsy, some paradoxical experimental data and outstanding questions have also been discussed.

Contents

1. Introduction

Epilepsy is a common, neurological disorder characterized by recurrent seizures that are unpredictable and sometimes progressively severe. Approximately 1% of the population has epileptic episodes at some point in their lives. To date, the treatment of epilepsy has generally been far from satisfactory because most current drugs mainly counteract

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membrane proteins that control neuronal excitability and mediate the end-stage symptoms of epilepsy, that is, the seizures themselves instead of targeting the primary signaling pathways that initially trigger the numerous downstream cellular and molecular mechanisms mediating epileptogenesis. Thus, the development of new approaches for the treatment of epilepsy has become an important challenge. The mammalian target of rapamycin (mTOR) signaling pathway has recently received attention as a logical candidate for treating epilepsy, due to its suggested pivotal role in many aspects of cellular functions that may influence neuronal excitability and mediate epileptogenesis. Hyperactivation of mTOR signaling has been demonstrated to be a common occurrence in epilepsy. Moreover, mTOR inhibitors, in particular, rapamycin, appear to have antiepileptogenic actions. Tuberous sclerosis complex (TSC), an important genetic cause of epilepsy, is probably the best model in studying mTOR deregulation, especially with regard to its role in epileptogenesis [1]. We also discussed the possible contributions of mTOR to other, more common types of epilepsy, such as acquired epilepsy [2,3]. Overall, we propose that mTOR inhibition is an exciting potential antiseizure and antiepileptogenic strategy.

2. The mTOR pathway overview and functional mTOR signaling in the brain

Mammalian target of rapamycin (mTOR), a conserved serine/threonine kinase and a member of the phosphatidylinositol 3-kinase-related kinase (PIKK) family, exists in two multi-protein complexes defined by the distinct protein binding partners with mTOR, namely, mTORC1, which is rapamycin-sensitive via its FK506-binding protein of 12 kDa (FKBP12) interaction [4], and mTORC2, which is largely insensitive to the effects of rapamycin (Fig. 1). The complex details of mTOR biology and mTOR pathway have been extensively reported elsewhere and are outside the scope of this review [5–9]. An intriguing finding in the last decade demonstrated that activation or inhibition of mTOR by upstream pathways is generally accomplished through opposing effects on a modulator between AKT and mTOR, which is formed by tumor suppressor proteins tuberous sclerosis 1 and 2 (TSC1 and 2). Various physiological or pathological stimuli converge on this hamartin (TSC1)/tuberin (TSC2) complex to regulate mTORC1 activity (Fig. 1). The inhibitory function of TSC1/TSC2 obligate heterodimer acts through TSC2's functional GAP domain. In addition, TSC1 protein stabilizes TSC2, thus preventing its degradation [10,11]. Of interest, patients with TSC2 mutations have a worse overall prognosis than those with TSC1 mutations [12], and induced TSC2 mutations in mice intrinsically caused a more severe neurological phenotype than TSC1 mutations [13]. The mTOR pathway is also negatively regulated by other upstream regulators, for example, phosphatase and tensin homolog (PTEN) and STE20-related adaptor protein α (STRADalpha). Mutations in these genes result in hyperactivity of the mTOR pathway associated with cellular alterations involving abnormal differentiation, growth and proliferation, with high comorbidity with epilepsy. The promising initial studies between mTOR and neurological diseases have demonstrated that mTOR and its signaling pathways have a significant impact on the nervous system. In the adult brain, mTORC1 supports neuronal activity by selective promotion or suppression of translation of mRNAs as well as regulation of neurotransmitter receptor expression [14,15]. Not surprisingly, the mTOR pathway is required for both (short-term) activity-dependent local protein synthesis

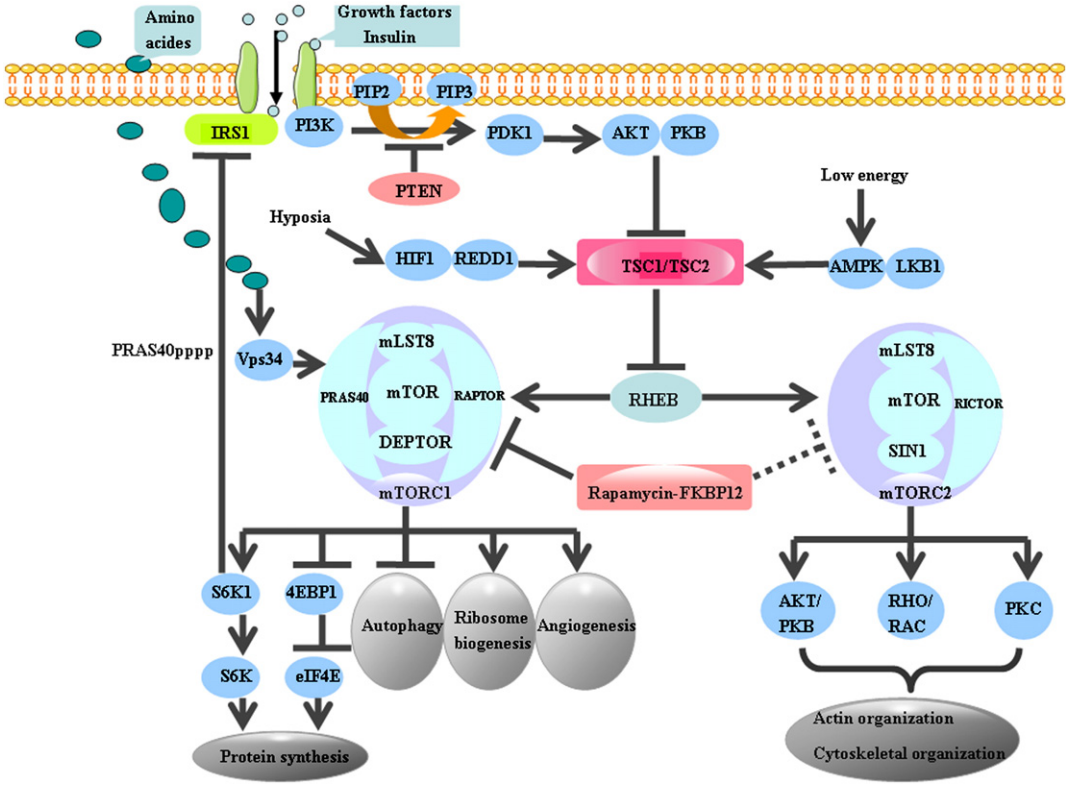

Fig. 1. Schematic representation of mTOR signaling pathways. Mammalian target of rapamycin (mTOR) exists in two multi-protein complexes, namely, mTORC1 and mTORC2. mTOR pathway is actively and negatively regulated by various physiological or pathological stimuli through various upstream signaling pathways and intermediary proteins (TSC1, TSC2, Rheb). The mTOR pathway acts on downstream effectors to inhibit autophagy as well as promote protein synthesis related to multiple functions, such as cellular homeostasis and other processes that may relate to epileptogenesis. Arrows and bars represent activation and inhibition, respectively. This schematic overview shows the most important factors of the mTOR signaling network. Not all members of the signaling pathway are illustrated in order to be simplified. The following abbreviations are used: AMPK = 5′ adenosine monophosphate-activated protein kinase; eIF4E = elongation initiation factor 4E kinases; REDD1 = regulated in development and DNA damage responses 1; HIF-1 = hypoxia-inducible factor 1; Raptor = regulatory-associated protein with TOR; Rictor = rapamycin-insensitive companion of mTOR; VSP34 = class III phosphoinositide-3 kinase vacuolar protein sorting 34; mLST8 = mammalian lethal with sec 13 mLST8; PRAS40 = proline-rich Akt/PKB substrate 40 kDa PRAS40; Sin1 = SAPK interacting protein 1; Deptor = DEP-domain containing mTOR-interacting protein.

and (long-term) synaptic plasticity [16], since both of them depend on protein synthesis (Fig. 2) for sustained changes in synaptic strength [17–19]. mTORC1 activation can result in translation of additional mRNAs, which have specific roles in synaptic function and plasticity, including NR1, CamKIIalpha, PSD95, Arc, and PKM zeta [18,20,21]. mTOR is critical in neuronal development as evidenced by its crucial role in axon and dendrite developments, and dendritic spine morphogenesis [22–25]. The role of mTOR in the regulation of neuroendocrine through the hypothalamic axis has also been described [26,27]. Neurons can take advantage of the mTORC1 pathway to produce long-term changes to various signals due to its properties of rapidly and selectively translate mRNAs. This suggests that mTORC1 may also involve in other potential brain-specific functions. For example, a previous study has demonstrated that the TSC-mTOR pathway is required for the function of appetite-suppressing neural circuits and abnormal mTOR pathway in the CNS might be responsible for the development of obesity [28]. mTORC1-mediated translation in the SCN (the suprachiasmatic nucleus) is also suggested to play crucial roles in the circadian entrainment [29]. Recent studies suggest that the PI3-K/Akt/mTOR pathway may regulate acute nervous system injury and subsequent neurodegeneration [30–33], although the role of the PI3-K/Akt/mTOR pathway can be variable and may require activation to promote neuronal survival [34–38]. It is reasonable to hypothesize that mTOR may be involved in the aberrant axonal sprouting and neurogenesis implicated in epileptogenesis based on the role of mTOR in neuronal development and plasticity. Crucial for the successful translation of mTOR into robust and safe clinical strategies will be the further elucidation of the complex roles that these signaling pathways hold in the nervous system. Notably, some diseases or animal models caused by genetic mutations in the molecules on the mTOR pathway show epileptic seizures and neurological abnormalities (Table 1). Mutations of TSC genes, for example, via downstream effects on neuronal and synaptic structures or neurotransmission, can induce fundamental alterations in network properties, and an imbalance between excitation and inhibition, producing epilepsy, mental retardation, and autism. mTOR dysregulation in the pathogenesis of acquired epilepsy has also been supported by increasing evidence (Tables 2 and 3).

3. mTOR inhibition

Detailed descriptions of the characteristics of mTOR inhibitors have been extensively reported elsewhere and only an overview of these compounds will be provided here (Fig. 3). mTOR inhibitors are currently approved or being tested in clinical trials for epilepsy treatment due to the fact that mTOR inhibitors appear to have antiseizure and antiepiloptogenic actions via regulation of protein synthesis and other cellular processes (Fig. 4). Rapamycin (sirolimus), a macrolide lactone, binds to and inhibits mTOR kinase activity. Only recently has the anti-epilepsy potential of rapamycin become widely appreciated. Limitations in the solubility and pharmacokinetic properties of rapamycin have driven efforts to identify and manufacture rapamycin analogs (rapalogs) with more favorable pharmaceutical characteristics including temsirolimus (CCI-779), everolimus (RADD001), and ridaforolimus (AP23573) [39]. Based on clinical trials [40], everolimus has been approved by the U.S. Food and Drug Administration for treatment of SEGAs (subependymal giant-cell astrocytomas) in TSC patients, who are not candidates for surgical resection in November 2010. Although everolimus has also been shown to lead to a number of side effects that include treatment-related oral and respiratory infections, stomatitis, and leukopenia and to potentially result in increased seizure frequency which observed in a minority of patients [40], no patients discontinued

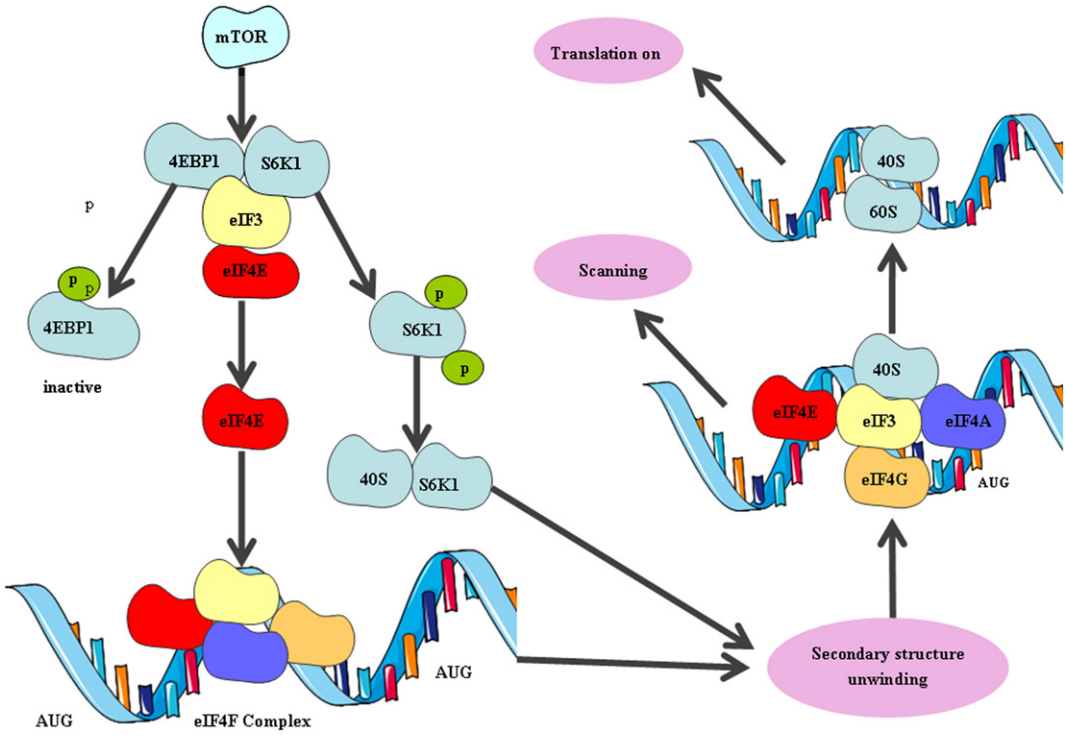

Fig. 2. Mechanism of the cap-dependent translation of mRNA. Under basal conditions, ribosomal S6 kinase (S6K1) and elongation factor 4E binding protein-1 (4EBP1) are bound to eukaryotic initiation factor 3 (eIF3) and the complex remains inactive. In response to growth stimulation, mammalian target of rapamycin (mTOR) binds to eIF3 and phosphorylates S6K1 and 4EBP1. mTOR phosphorylates several sites in 4E-BP1 which binds to and inhibits the eukaryotic initiation factor 4E (eIF4E), which is rate-limiting for cap-dependent translation. 4E-BP1 then dissociates from eIF4E, facilitating formation of the eIF4Fcomplex containing eIF4E, which binds to the 7-methylguanosine cap present on the 5′ end of mRNAs, the eukaryotic initiation factor 4A (eIF4A), the eukaryotic initiation factor 4G (eIF4G) and eIF3 to initiate cap-dependent mRNA translation. Similarly, mTOR phosphorylates S6K1, activating the kinase activity of S6K1 by causing its dissociation from the eIF3 complex. The molecular details of many of these mechanisms remain to be defined, but their corecruitment increases mRNA binding and finally stimulates protein synthesis initiation supporting cell metabolism, growth, and angiogenesis. Arrows represent activation, whereas bars represent inhibition.

Table 1
Known involvement of the mTOR pathway in epilepsy.

Gene	Role and function	Animal models or diseases which are associated with epilepsy	Pathophysiological or clinical manifestations related to the CNS	Refs.
TSC1 (hamartin), TSC2 (tuberin)	The TSC1/2 complex has been found to play a crucial role in the mTORC1 pathway. TSC2 physically interacts with RICTOR, activating mTORC2 activity.	Astrocyte-specific $TSC2^{HGFAP}$ knockout mice	These animals exhibited enlarged cells, megalencephaly and astrocytosis, and started dying after 3 weeks old. (These mice confirmed that loss of function of Tsc2 in radial glial progenitors is one initiating event in the development of TSC brain lesions and the importance of Tsc2 in the regulation of neural progenitor pools).	[121]
		Neuron-specific TSC1 knockout ($TSC1^{synI}$) mice	These mice showed several neurological abnormalities beginning at postnatal day 5 with median survival of 35 days, and seizure episodes.	[122]
		Tsc1 CKO mice in GABAergic interneuron progenitor cells	GABAergic interneurons of CKO mice are enlarged and show increased mTORC1 signaling, reduced GABAergic subtypes, and impaired interneuron migration.	[123]
		Rictor CKO mice	The mice are hyperactive with reduced anxiety-like behavior. The cerebral cortex shows decreased white matter and increased levels of monoamine neurotransmitters. This mice model reveals that mTORC2 may contribute to some of the neurologic manifestations seen in TSC.	[66]
		A rat model carrying a spontaneous TSC2 mutation (Eker rat, $TSC2^{+/-}$)	These rats showed impaired LTP and LTD in the hippocampus as well as enhanced episodic-like memory.	[124,125]
		$Tsc2^{GFAP1}$ CKO mice	Enlarged cells, megalencephaly, astrocytosis.	[13]
		Tuberous sclerosis	Epilepsy, tubers, autism, cognitive impairment, tumors.	[126,127]
		Focal cortical dysplasia IIB	Focal cortical dysplasias, epilepsy.	[100]
PTEN (phosphatase and tensin homolog)	PTEN is an important regulator of cell growth and survival, and negatively regulates the PI3K–AKT–mTOR pathway via converting PIP3 to PIP2.	Cowden syndrome	Macrocephaly (38%), epilepsy, ataxia, intellectual disability.	[128]
STRADalpha (STE20-related adaptor protein α)		Polyhydramnios, megalencephaly, symptomatic epilepsy syndrome (PMSE)	Epilepsy, macrocephaly, cognitive disability, subependymal dysplasias.	[129,130]
PIM-1 (provirus integration site for Moloney murine leukemia virus)	This kinase activates mTORC1 activity via phosphorylating PRAS40 on Thr246 which causes the release of PRAS40 from mTORC1. The kinase can also inhibit mTORC1 activity via phosphorylating AMPK at Thr172.	Kainate rat model	PIM-1 is increased in dentate gyrus.	[131]
HSP70 (heat shock protein 70)	HSP70 interacts with RICTOR and TSC1/2 complex.	HSP70-1/HSP70-3 double knockout mice	These mice become more susceptible to ischemia-induced damages.	[132]
AKT (acutely transforming retrovirus AKT8 in rodent T cell lymphoma)	After phosphorylation, AKT regulates different cellular processes which include cell growth, cell proliferation, apoptosis, and glucose metabolism.	AKT1 null mice	These mice presented impaired adult neurogenesis and LTP in the hippocampus.	[133]
		AKT2 null mice	These mice showed abnormality in glucose metabolism.	[134]
		AKT3 null mice	These mice showed smaller brains and reduced phosphorylation level of S6.	[135]
		$Akt3^{Nmf350}$, dominant mutant mice	Paradoxically, these mice exhibited enlarged brain, increased phosphorylation of S6, and are more susceptible to seizure.	[136]
ERK1/2 (ERK1 = p44 mitogen-activated protein kinase (MAPK), ERK2 = p42 MAPK1)	Ser/Thr kinases of Ras/MAPK signaling pathway which are particularly involved in neuronal and synaptic plasticity.	Pilocarpine-induced SE or kainate-induced SE	The activation of ERK is increased during chronic seizures.	[137]
		Kainate-induced SE	Activated ERK phosphorylates Kv4.2, thus decreasing the surface expression of the channel and dendritic A current in SE.	[138]

CKO = conditional knockout, SE = status epilepticus, LTP = long-term positive, LTD = long-term depression, mTOR = mammalian target of rapamycin, Rictor = rapamycin-insensitive companion of mTOR.

everolimus treatment because of adverse events which were mostly grade 1 or 2 in a very recently double-blind, placebo-controlled, phase 3 trial of 117 patients [41]. Recently clinical data showed that everolimus is effective and safe in infants and young children with epilepsy and SEGAs associated with TSC, which offers a valuable treatment option [42]. The search for selective agonists targeting specific effectors of the mTOR pathway has led to the discovery of two new inhibitors of mTOR, respectively, PI3K/mTOR dual inhibitors which bypass feedback loops, potentially increasing their efficacy compared with rapalogs [43,44] and mTOR C1/2 inhibitors which probably have more undesirable side effects than rapamycin as these compounds strongly inhibit both mTORC1 and mTORC2 [45,46]. ketogenic diet, a high fat and low carbohydrate diet, is well-established treatment for epilepsy [47]. Interestingly, the hippocampus and liver of normal rats which were fed ketogenic diet demonstrated reduction in the expression of two markers of mTOR pathway activation, phosphorylated ribosomal protein S6 (pS6) and phosphorylated acutely transforming retrovirus AKT8 in rodent T cell lymphoma (pAKT), suggesting that the mTOR pathway may be responsible for the effects of the ketogenic diet on growth and seizures [48]. A few intriguing studies have recently suggested two novel representatives of mTOR inhibitors, respectively, curcumin [49,50] and resveratrol [51–53], which possess antioxidant, antiinflammatory, and anticancer

Table 2
Studies on the effects of rapamycin treatment on the representative animal models of genetic epilepsy.

Animal model	Time and administration of treatment	Antiepileptogenic			Anti-pathophysiological abnormalities				Refs.
		Inhibit seizures	Inhibit epilepsy development	Improve survival	Inhibit cognitive deficits	Inhibit cell size/number	Inhibit megalencephaly	Inhibit other	
$Tsc1^{GFAP}$ CKO mice	Postnatal day 14 (~2 weeks presymptomatic)	Yes (showed delay in onset, decrease in frequency and duration, milder seizure type).	Yes	Yes	–	Yes	Yes	Reduction of Glt-1 expression	[74]
$Tsc2^{GFAP1}$ CKO mice	Postnatal day 14 (presymptomatic)	–	Yes	Yes	–	Yes	Yes	Neuronal dispersion	[13]
$Tsc2^{+/-}$ mice	Adult	–	–	–	Yes	–	–		[77]
Synapsin-Tsc1 CKO mice	Postnatal days 7–9	–	Yes	Yes	–	Yes	–	Neurofilament expression and phosphorylation Impaired myelination	[75]
Tsc2 KD in mouse neural progenitor cells (mNPCs) in vitro and vivo	Embryonic days 15–18	–	–	Yes	–	Yes	–	Altered cortical lamination, brain weight and body size. (These results suggest firstly that using rapamysin during embryogenesis could prevent abnormal brain development in TSC.)	[139]
Tsc1cc Nes-cre^{+} mouse model	Embryonic days 15–17, postnatal day 8	–	–	Yes (with a median survival of 10 days and maximum of 20)	No	No	No	Body weight	[82]
NS-Gfap-Pten CKO mice	Postnatal 4 weeks (symptomatic)	Yes (as early as 4 weeks)	–	–	Yes	Yes	Yes	Aberrant mossy fiber sprouting, Pten expression in dentate gyrus (within days after birth)	[92]
Nse-Pten CKO mice	Age 5–6 weeks (presymptomatic phase)	–	–	–	Yes	Yes	Yes	Hypertrophy of hippocampal granule cell and cortical neuron	[89]
	Age 10–12 weeks (symptomatic)	Yes (around 10 weeks of age or later).	–	–	–	Yes	Yes	Pten expression in dentate gyrus (not complete until the fourth postnatal week)	

– = not applicable or not done, PTEN = phosphatase and tensin homolog deleted on chromosome ten, TSC1 = tuberous sclerosis complex 1 protein, TSC2 = tuberous sclerosis complex 2 protein, TSC = tuberous sclerosis complex, CKO = conditional knockout.

Table 3
Effects of mTOR inhibitors in animal models of acquired epilepsy.

Model	Time of administration and duration of treatment	Inhibit mossy fiber sprouting	Inhibit other pathophysiological or clinical manifestations	Inhibit seizures	Inhibit epilepsy development	Refs.
Multiple-hit rat	After the onset of spasms.	Not applicable	Cognitive deficits	Inhibit spasms	No	[3]
Kainic-acid induced SE in rats	3 days before SE or 24 h after SE, up to 7 weeks.	Yes	Neurogenesis	Only showed decrease in frequency, no acute effects on behavioral seizures.	Yes	[140]
Pilocarpine-induced SE in adult rats	>10 weeks after SE when spontaneous seizures occur, 3 weeks.	Yes		Showed decrease in frequency and duration, as well as milder seizure type.	Seizures recur after rapamycin discontinuation. No increase in proportion of animals that become seizure free.	[94]
Pilocarpine induced SE in mice	Starting 1 day after SE, entire period.	Yes		No	No	[111]
Amygdala stimulation model of TLE in rats	Starting 1 day after SE, 2 weeks.	No		Not done	No	[112]
Pilocarpine induced SE in mice	Starting 1 day after SE for 6 consecutive days, then every other day entire period.	Yes	Frequency of spontaneous EPSCs (excitatory postsynaptic currents), amplitude of antidromically evoked EPSCs.	Yes	Not done	[141]
Pilocarpine-induced SE in rates	Starting 2 weeks after pilocarpine-induced SE, then every other day for a total of 4 treatments per rat.	Not done	Spatial learning and memory deficits, dendritic dysregulation.	Not done	No	[110]
Hypoxia-induced seizures in rats	Starting 24 h before and 1 h after exposure to hypoxia.	Not applicable	Autistic-like behavior, glutamatergic, neurotransmission.	Yes	Yes	[142]
WAG/Rij rats (absence epilepsy model)	Age 45 days, 17 weeks (early chronic). Age 6 months, 7 days (both acute and sub-chronic).	Not applicable	Anti-absence, anti-inflammation.	Yes	Yes	[118]

SE = status epilepticus, TLE = temporal lobe epilepsy.

properties. Curcumin has been shown to retard epileptogenesis in a model of posttraumatic epilepsy [50]. Rapamycin shows significant promise in animal models as an antiepileptogenic and antiseizure agent for the treatment of epilepsy. However, recently experimental data in immature and adult rats using different seizure models and treatment paradigms suggest that rapamycin is a poor anticonvulsant and may have beneficial effects only against epileptogenesis, which also present new insights into mechanisms of rapamycin action on seizures indicating a possible connection between mTOR signaling and neuropeptide Y (NPY) system [54]. In agreement with these data, the available clinical data has suggested that antiseizure efficacy of rapamycin is relatively modest, with most patients still experiencing seizures. The significant side effects of rapamycin also limit its long-term utility in humans, such as the suppression of the immune system and associated opportunistic infections [55], dermatological adverse events [56–58], and metabolic changes [56,59,60]. Treatments with rapalogs or mTOR kinase inhibitors also have additional limitations [61,62].

4. The role of mTOR in epilepsy and epileptogenesis

4.1. The role of mTOR signaling pathway in genetic epilepsies

Multiple animal models of genetic epilepsies have been generated by specific disruption of the Tsc1, Tsc2 or Pten gene, and a critical role of the mTOR pathway in epileptogenesis as well as the beneficial efficacy of rapamycin in epilepsy have been firmly established in many of these models (Table 2).

4.1.1. Tuberous sclerosis complex (TSC) as a prime example of mTOR dysregulation in epileptogenesis

Among the genetic causes of epilepsy, tuberous sclerosis complex (TSC) is an attractive model given the fact that probably the strongest link between mTOR and epilepsy is in it. TSC, an autosomal dominant disorder, results from mutations in either the TSC1, located on chromosome 9q34 [63], or the TSC2, located on chromosome 16p13.3 [64]. These two genes encode a 130-kDa protein TSC1/hamartin or a 200-kDa protein TSC2/tuberin respectively, which binds to each other via their respective coiled-coil domains to form a functional heterodimer (TSC2:TSC1) [65]. The clinical utility of mTORC1 inhibitors has received attention for a variety of TSC manifestations, stimulated by the knowledge that hyperactivation of mTORC1 pathway occurs in all cells lacking either TSC1 or TSC2. The contribution of decreased mTORC2 signaling to neural development and homeostasis has been studied in a conditional knockout (CKO) of Rictor, a key component of mTORC2, in which also reveals the contribution of mTORC2 signaling to TSC [66]. However, the specific mechanisms of seizure generation in TSC are poorly defined. Cortical tubers are focal developmental malformations of the cerebral cortex exhibiting loss of normal hexalaminar structure and containing several abnormal cellular elements including dysmorphic neurons (DNs), excessive numbers of astrocytes, and giant cells (GCs) [67], which are found in 80–90% of patients [68]. Some suggest that cortical tubers are the primary site of epileptogenesis given the fact that seizures clearly originate from radiographically identified tubers and surgical resection of tubers can alleviate seizures in patients with medically intractable epilepsy [69–71]. However, recent data have raised some controversy [72]. Some patients continue to seize following tuberectomy [71]. A recent study of three TSC patients who underwent detailed intracranial electrocorticography revealed that epileptogenicity is not likely to originate from the lesion, but rather its surrounding perituberal cortex [73]. Therefore, there is an urgent need to identify the mechanisms involved in the transition from the interictal state to seizures, in order to develop novel strategies to prevent ictogenesis. Several mouse models of TSC have been generated which exhibit many of the pathologic features of TSC, in particular, including megencephaly, neuronal hypertrophy, astrocytosis, and impaired myelination, which are reversed by the mTOR inhibitor, rapamycin [74–76]. Postnatal treatment with mTOR inhibitors in symptomatic mice decreased seizures (i.e., antiseizure) [74,77] or prevented the development of epilepsy and the underlying molecular and histopathological mechanisms of epileptogenesis (i.e., antiepileptogenic) [13,74,75] in presymptomatic mice. In addition, there have been strong clinical evidences that both rapamycin and everolimus decrease seizures in TSC patients with established epilepsy [40,78,79]. Vigabatrin (VGB), a drug which particularly effective for seizures in TSC patients, has been identified to inhibit mTOR pathway activity. And this intriguing effect could represent an additional mechanism of action that may account for the distinctive efficacy of VGB in TSC

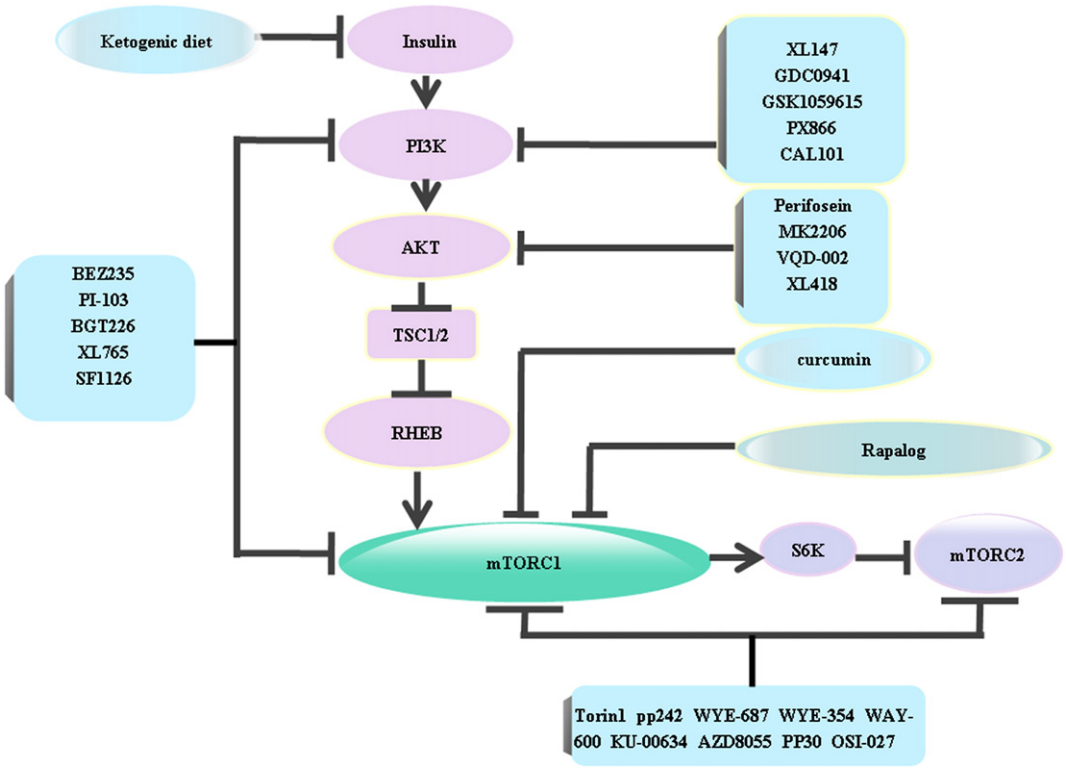

Fig. 3. Pharmacologic inhibitors of PI3K-AKT-mTOR signaling pathway. Rapalogs, PI3K/mTOR dual inhibitors, mTOR C1/2 inhibitors, PI3K inhibitors, AKT inhibitors and 2 new representatives of mTOR inhibitors, respectively, curcumin and ketogenic diet. Arrows represent activation, whereas bars represent inhibition.

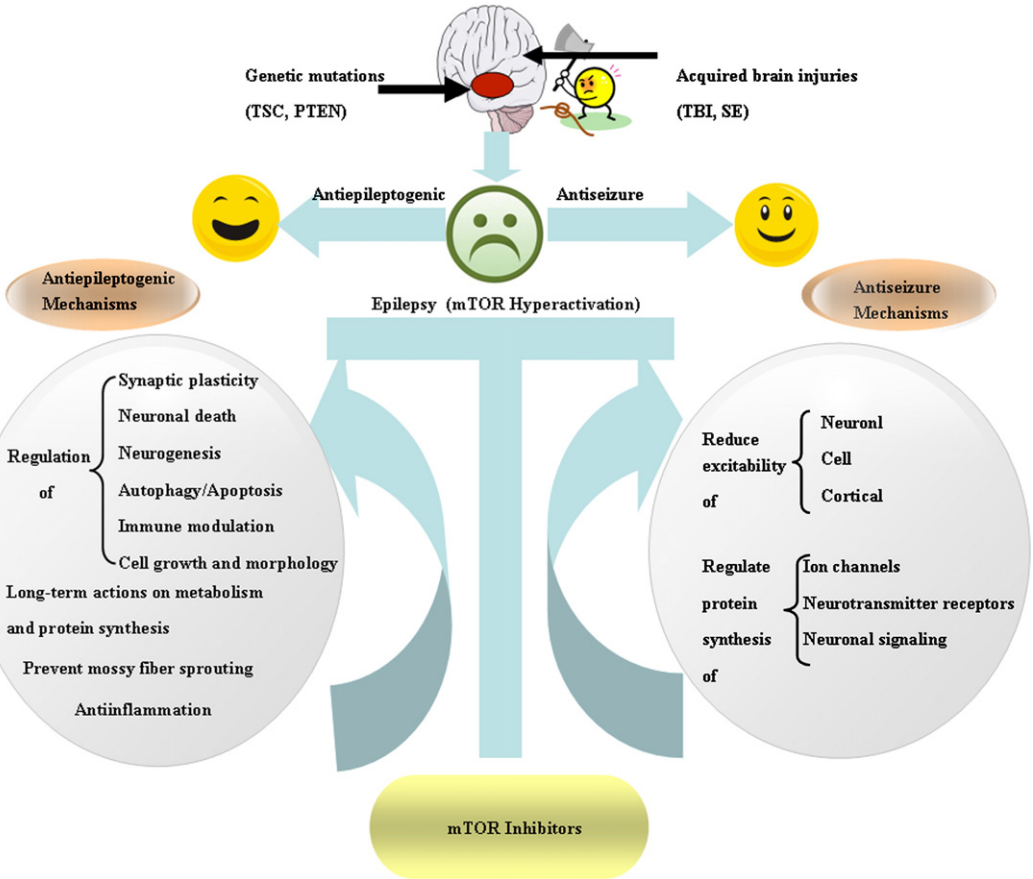

Fig. 4. Mechanisms of mTOR inhibition in antiseizure and antiepiloptogenic. Hyperactivation of mTOR signaling has been demonstrated to be a common occurrence in various types of epilepsy, including those induced by genetic defects or acquired injuries. mTOR inhibitors appear to have antiseizure and antiepiloptogenic actions via regulation of protein synthesis and other cellular processes. mTOR inhibitors represent a promising therapeutic option for the treatment of epilepsy. Arrows represent activation, whereas bars represent inhibition. Abbreviations: TSC = tuberous sclerosis complex; TBI = traumatic brain injury; SE = status epilepticus.

[80]. mTOR inhibitors have become the clinical recommendations for the management of SEGAs, which is a type of brain tumor that develops in 10–15% of individuals with TSC [81]. Prenatal treatment with rapamycin has been explored firstly in a new fetal brain model of TSC (Tsc1cc Nes-cre + mouse model). A single dose of prenatal rapamycin to pregnant dams increased survival of mutant mice but did not prevent the continuing severe manifestations, including developmental delay, neurological symptoms, and eventual lethality of the mutation [82]. Continued, long-term treatment with rapamycin is required for either the antiseizure or antiepileptogenic benefit because once rapamycin is withdrawn, mTOR hyperactivation triggers epileptogenesis again. These values and limitations of rapamycin lead to a recommendation for caution in consideration of using it in the treatment of TSC.

4.1.2. The role of mTOR signaling pathway in focal cortical dysplasias (FCD)

Due to the similarities in histopathology and cell signaling abnormalities between TSC and FCD, it is likely that new insights into FCD associated with epilepsy, cognitive, disability, and autism will follow with our advanced understanding of the neurobiology of TSC.

FCD has a male sex predominance in pediatric patients, which is unlike the other etiologies of medically intractable epilepsy [83]. According to a new three-tiered classification system of FCD, three distinct types can be differentiated: CDI, CDII, and CDIII [84]. FCD with balloon cells (FCDIIB) is of particular importance in the context of the mTOR pathway [84]. Both pathological and clinical observations of FCDIIB led us to suggest that mTOR dysregulation probably contributes to abnormal cell size and differentiation in it. For example, balloon cells which are morphologically similar to the giant cells of TSC, show increased levels of pS6, although these cells are derived by distinct pathogenic mechanisms [85] and recruit different PI3K molecular cascades [86]. In addition, cytomegalic neurons show mTOR hyperactivation as well [87]. FCDIIB are also associated with particularly severe epilepsy and high rates of intractability [69,88]. However, recently created models have not been able to replicate FCDIIB accurately.

The link between mTOR and FCD is further elucidated in the study of Pten (phosphatase and tensin homolog deleted on chromosome ten) mutant animal models. Rapamycin is also effective for the treatment of mTOR hyperactivation induced by mutation of Pten, suggesting that it may prove useful in the treatment of FCD patients. For example, rapamycin can decrease seizures and associated pathological abnormalities, in addition to improving survival and social deficits suggestive of autism [89–91]. Furthermore, subsequent intermittent rapamycin treatment was able to maintain a more long-term antiseizure effect than in TSC models [92].

4.2. The role of mTOR signaling pathway in acquired epilepsies

There is a high comorbidity of the acquired disorders with epilepsy. Acquired epilepsies are characterized of a latent period after the insult before the onset of seizures during which activation of the mTOR signaling pathway could represent one of the initial signals and trigger downstream effects in the brain that cause seizure generation. In addition to specific genetic and developmental epilepsies, experimental evidences for the involvement of the mTOR pathway in epileptogenesis and the rational therapeutic efficacy of rapamycin have also been obtained in animal models of different types of acquired epilepsy (Table 3). Inhibition of the mTOR pathway leads to alleviation of the neuropathological changes induced by epileptogenic stimuli including status epilepticus (SE) and traumatic brain injury (TBI), such as mossy fiber sprouting, neurodegeneration, and neurogenesis [2,93,94]. As neuroprotective agents for acquired brain injuries, mTOR inhibitors play a broader role in some detail which is independent of epilepsy mentioned above [25,95]. Inhibition of mTOR-mediated apoptotic pathways and reduction of cell death could potentially contribute to neuroprotection effects of mTOR inhibitors in response to brain injury. mTOR inhibitors could also inhibit autophagy during seizure and restore autophagic balance to the intracellular system, executing its neuroprotection roles via allowance of neurons to remain functional in the face of rising levels of stress in seizure. Furthermore, immunophilin ligands of rapamycin can modulate Ca^{2+} channels and protect neurons from Ca^{2+} induced cell death. Various models of brain injury have demonstrated neuroprotection roles of mTOR inhibitors such as neonatal hypoxia–ischemia [96], traumatic brain injury [97], and kainic-acid induced status epilepticus (SE) [2].

4.2.1. The role of mTOR signaling pathway in infantile spasm (IS) epileptogenesis

Around 200 human disorders [98], including these genetic "TORopathies", which are shown in the previous section, such as FCDIIB [88,99,100], TSC [101–103], and Pten models [104,105], and which are associated with dysregulated mTOR pathway, have been linked to IS. The relatively high comorbidity between IS and these genetic "TORopathies" is maybe because of the shifting of the onset of associated epilepsy to the early ages of life when IS is a highly prevalent seizure type. However, the work published by Galanopoulou's lab has recently firstly indicated a direct antiseizure as well as a disease-modifying effect of rapamycin in IS of nongenetic etiology, using the multiple-hit rat model of symptomatic IS [3]. Rapamycin not only decreased the frequency of pre-existing spasms in neonatal rats, but also decreased the subsequent development of cognitive deficits observed in this model, suggesting that mTOR signaling is involved in their generation. Notably, early suppression of spasms with the therapeutically effective rapamycin doses sufficed to stop spasms without the requirement of continuous administration of rapamycin, indicating that rapamycin could be given only during the acute phase of spasms instead of chronic exposure to the drug in the treatment of IS of acquired etiology. Of interest, rapamycin had no effect on the development of other non-spasm seizure types and it suggests that the networks mediating spasms are distinct from those implicated in other seizures. Furthermore, in another model of "cryptogenic" spasms, rapamycin had no anticonvulsant effect [106]. However, the same dose of rapamycin was effective against the spasms in a model of symptomatic infantile spasms [107], indicating that in light of the type and cause of epilepsy or the timing of rapamycin administration, the role of the mTOR pathway in epileptogenesis may vary. It is also necessary to test the safety profile of mTOR inhibitors, especially if given during the sensitive infantile period.

4.2.2. The role of mTOR signaling pathway in status epilepticus (SE) injury models

SE-induced epilepsy models are ideal models to demonstrate antiepileptogenic effects of rapamycin except the TSC models, which are not simply seizure-suppressing epilepsy. In the kainate rodent model of epilepsy, rapamycin, administered prior to the onset of spontaneous seizures, blocks both phases of mTOR activation and correspondingly reduces mossy fiber sprouting, neuronal death, neurogenesis, as well as decreases the subsequent frequency of spontaneous seizures. In addition, treatment with rapamycin 1 day after status epilepticus can block the second phase of mTOR hyperactivation and decrease mossy fiber sprouting and subsequent seizures, although it has no effect on neuronal death and neurogenesis [2]. This suggests that rapamycin has antiepileptogenic actions in this model. However, when administered within 1 h of kainate, rapamycin causes paradoxical exacerbation of kainate-induced mTOR activation which is associated with greater neuronal death several days after kainate status epilepticus. Thus, it appears that rapamycin causes a paradoxical activation of the mTOR pathway under limited circumstances and, consequently, rapamycin may have dual, opposing effects on cell death. This needs to be considered in clinical therapy for epilepsy due to the potential adverse effects on neurological status [108]. SE which is induced by pilocarpine longer than 1 h results in the development of epilepsy, and this finding may provide a time-window for optimal seizure intervention and epilepsy prevention

[109]. In the pilocarpine model, rapamycin can prevent mossy fiber sprouting, but like the TSC animal studies, maintenance of this suppression also requires the constant presence of rapamycin, and rapamycin treatment did not reverse already established axon reorganization [93]. Rapamycin can suppress seizure frequency remarkably in a pilocarpine model in rats which were documented to have spontaneous seizures [94]. Although without the usage of EEG monitoring, this reported effect seems quite robust. The mediated action of mTORC1 hyperactivity as well as the beneficial effect of rapamycin on the behavioral deficits and dendritic pathology associated with SE have been evaluated in pilocarpine-induced SE rat model [110]. Together, these results suggest that there is a wide therapeutic window of opportunity for mTOR inhibitors in acquired epilepsy. However, other recent studies have found paradoxical effects of rapamycin in epilepsy treatment [108,111,112], which suggest a complex, potential dual regulation of epileptogenic mechanisms by mTOR. A recently published study reported no effect of rapamycin post-treatment on either the epilepsy development or the latency period of spontaneous seizure onset in the amygdala stimulation model [112]. In a word, more experimental work is needed to clarify the specific mechanisms by which rapamycin exerts its antiepileptogenic and antiseizure actions as well as to determine the corresponding timing and clinical applications of rapamycin for epilepsy.

4.2.3. The role of mTOR signaling pathway in other etiologies of epilepsy

Recent studies have found mTOR hyperactivation and neuroprotective effects of mTOR inhibitors in other etiologies of epilepsy, such as in traumatic brain injury (TBI) [97,113], in neonatal hypoxia–ischemia injury [114], and in rapid electrical kindling injury [115]. However, whether mTOR inhibitors have the antiepileptogenic potential in these settings needs further research.

TBI is one of the main causes of medial temporal lobe epilepsy (TLE) [116]. Rapamycin might have antiseizure and possibly antiepileptogenic effects in post-SE rat models [2,94] which is mentioned above and in which TLE develops after a latent period of several weeks. In both the animal model of TLE and the sclerotic hippocampus from patients with drug resistant TLE, the reactive astrocytes are presented with the most prominent mTOR activation [117]. Rapamycin has also been very recently proved to possess anti-absence and anti-inflammatory properties in a well-established animal model of absence epilepsy [118].

5. Targeting the mTOR signaling pathway for epilepsy therapy: a double-edged sword?

Yet, for the effective translation of this molecular target into robust clinical entity directed against epilepsy over the next 5 to 10 years, a number of questions that have arisen from current investigations need to be addressed. Presently, genetic epilepsies, especially TSC, represent the most obvious application for mTOR inhibition that is closest to clinical use for epilepsy. Clinical studies from TSC patients are limited, consisting simply of uncontrolled data supporting an antiseizure effect of mTOR inhibitors in TSC patients with established epilepsy [40,78,79]. Many patients with TSC may represent appropriate candidates for an antiepileptogenic drug trial given the high rate of epilepsy, the ability to diagnosis, and the medical refractory nature of epilepsy in TSC patients. Besides clinical data on efficacy for TSC patients, the requirement for long-term treatment of mTOR inhibitors is the other potential barrier as TSC is a genetic disease and mTOR inhibitors do not correct the underlying genetic defect driving mTOR hyperactivation. In addition to significant side effects which are mentioned above, mTOR inhibitors, at least in theory, may interfere with critical developmental and learning mechanisms in the brain, such as synaptic plasticity and long-term potentiation [19]. There is hope from animal model studies that the intermittent use of mTOR inhibitors can maintain efficacy, but reduce the risk of side effects [119,120]. The field in the potential impact and application of mTOR inhibitors for acquired epilepsy is still in infancy, with no published clinical data addressing whether mTOR inhibitors are effective in non-TSC epilepsy. Although the use of mTOR inhibitors can reverse some of these epileptogenic processes in the limited primarily animal model studies in this regard, these effects depend upon the dosing and timing of administration as well as the animal model or species of epilepsy used (Table 4). Unlike TSC, in theory, antiepileptogenic therapy may be effective when applied for a limited time following acquired epilepsy, as some epileptogenic mechanisms may only occur for a limited, critical period after the initial brain injury. However, the beneficial effects of rapamycin appear to reverse upon discontinuation of the drug, at least suppression actions of late seizures and mossy fiber sprouting in the pilocarpine model [93,94]. mTOR inhibitors may have "epileptostatic" effects based on studies in genetic and acquired animal models, preventing the development of epilepsy-related pathology and, in certain cases, the development of epilepsy itself, with the requirement for chronic treatment to maintain efficacy. Furthermore, the risks of inhibiting mTOR after brain injury are necessary to be assessed, given that many mTOR-dependent processes could be compensatory and beneficial for recovery from brain injury. mTOR signaling probably lacks specificity and is not a good therapeutic target given that it possesses so many far reaching potential effects on the brain. Therefore, human use in clinical trials of such drugs for the management of established refractory epilepsy syndromes or for the prevention of epilepsy development following brain insult or injury still seems difficult considering these evident barriers mentioned above, and in any case, it is advisable to be cautious in their use.

Table 4
Variable effects of mTOR inhibitors which depend on certain factors in acquired animal models.

Certain factor	Animal model	Effect on epilepsy	Refs.
Time at administration	Pilocarpine-induced SE in rates	Early rapamycin treatment inhibited mossy fiber sprouting, but that later treatment which began after mossy fiber sprouting had developed for 2 months did not reverse established sprouting.	[93]
	Kainic-acid induced SE in rats	Rapamycin pretreatment for three consecutive days before kainate injection was able to decrease cell death, neurogenesis, mossy fiber sprouting, and reduce seizure frequency. By contrast, rapamycin treatment initiated 24 h after kainate-induced SE blocked the delayed activation of mTOR and inhibited mossy fiber sprouting but had no effects on neuronal death and neurogenesis; it also reduced seizure frequency, but less efficaciously than pretreatment.	[140]
Dose at administration	Multiple-hit rat	Very high doses (6 mg/kg, i.p.) suppressed spasms and normalized pS6-ir acutely, whereas low and moderate doses (1–3 mg/kg, i.p.) decreased spasms and pS6-ir but with a few days delay, depending on the dose.	[3]
Seizure types	Multiple-hit rat	Rapamycin only suppressed DLP spasms. Rapamycin did not appear to modify the frequency of other types of seizures.	[3]
Species	Pilocarpine-induced SE in adult rats	Rapamycin treatment for 3 weeks suppressed seizure activity (−93%); the effects were already observable after a few days, with a reduction of both seizure frequency and severity.	[94]
	Pilocarpine-induced SE in mice	Rapamycin dose-dependently suppressed mossy fiber sprouting in mice. However, rapamycin treatment did not affect seizure development or seizure frequency.	[111]

DLP = doxorubicin/lipopolysaccharide/p-chlorophenylalanine, SE = status epilepticus.

6. Conclusions and future perspectives

Epilepsy is one of the most critical medical, social, and economic problems confronting contemporary society. Data reviewed above provide a rationale for the therapeutic use of mTOR inhibitors in epilepsy. Our knowledge of rapamycin has evolved, over the past 40 years, from antifungal agent to parent compound for anticancer agent and to promising antiepileptogenic agent. Rapamycin has certainly taken researchers and clinicians on a rewarding journey which brought a promising strategy against the epilepsy. mTOR inhibitors represent a promising therapeutic option for the treatment of epilepsy, but to this premise is obtaining the answers of these tricky questions which are pitfalls in this process. For example, how can mTOR signaling be targeted to maximize efficacy but eliminate side effects? The key to balancing the efficacy and safety of mTOR inhibition may lie in the ideal pharmacological dose of mTOR inhibitors which prevents excessive pathologic mTOR activation but still allows normal physiologic mTOR activity. How to examine the presence of a critical therapeutic window between the initial precipitating injury and the subsequent development of epilepsy in animal models, as well as the minimal effective duration of treatment following the injury? Deeper understanding of the intricate signaling networks regulating mTOR activity as well as the precise underlying mechanisms of mTOR signaling pathway in epilepsy, and extensive preclinical modeling or experimental studies, also taking into account the identification and manufacture of new mTOR inhibitors with more favorable pharmaceutical characteristics, are expected to eventually lead to the effective translation of exciting preclinical findings into new therapeutic strategies for our patients suffering from epilepsy.

Conflict of interest

The authors declare that there are no any financial or personal relationships with other people or organizations that could inappropriately influence this work.

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