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mTOR as a potential treatment target for epilepsy

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Abstract

Current treatments for epilepsy suffer from significant limitations, including medical intractability and lack of disease-modifying or anti-epileptogenic actions. As most current seizure medications modulate ion channels and neurotransmitter receptors, more effective therapies likely need to target completely different mechanisms of action. The mammalian target of rapamycin (mTOR) pathway represents a potential novel therapeutic target for epilepsy. mTOR inhibitors can suppress seizures and prevent epilepsy in animal models of certain genetic epilepsies, such as tuberous sclerosis complex. mTOR inhibitors may also be effective in some models of acquired epilepsy related to brain injury, but these effects are more variable and dependent on a number of factors. Some clinical data suggest that mTOR inhibitors decrease seizures in tuberous sclerosis complex patients, but controlled trials are lacking and no clinical data on potential anti-epileptogenic actions exist. Future basic and clinical research will help to determine the full potential of mTOR inhibitors for epilepsy.

Keywords

epilepsy; rapamycin; seizure; tuberous sclerosis

Epilepsy affects approximately 1% of all people and involves significant morbidity and mortality. Treatment for epilepsy consists primarily of seizure medication, but current seizure medication suffers from a couple of significant limitations. While two-thirds of patients with epilepsy become seizure-free with medication, the remaining one-third continues to have seizures despite appropriate treatment and can be considered medically-intractable [1]. Furthermore, even when effective, currently available drugs appear to just suppress seizures as symptomatic therapy (antiseizure), but have not been proven to have disease-modifying effects to prevent the development or progression of epilepsy (anti-epileptogenic) [2]. As most current seizure medications modulate ion channels and neurotransmitter receptors, more effective therapies likely need to target completely different mechanisms of action [3]. The mammalian target of rapamycin (mTOR) pathway has recently been implicated in mechanisms of epileptogenesis and may represent a rational new drug target for epilepsy [4–6].

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The mTOR pathway

mTOR is a ubiquitous protein kinase involved in a number of important physiological processes, including cell survival, growth, proliferation and metabolism, as well as brain-specific functions, such as synaptic plasticity and cortical development [7–9]. mTOR combines with other regulatory and binding proteins to form at least two functional complexes, mTORC1 and mTORC2. mTORC1 can be acutely inhibited by the drug, rapamycin and other related mTOR inhibitors, whereas mTORC2 is relatively insensitive to rapamycin. However, prolonged exposure to rapamycin has been shown to inhibit mTORC2 [10]. mTORC1 primarily exerts its downstream functional effects via regulation of protein synthesis by controlling ribosomal proteins or translation-initiating factors (Figure 1). By comparison, mTORC2 acts predominantly through the regulation of a number of other protein kinases, such as Akt, and interactions with cytoskeletal elements of cells. In turn, the mTOR pathway responds to various physiological stimuli and environmental conditions via modulation by multiple upstream signaling elements. In particular, hamartin and tuberlin, proteins encoded by the *TSC1* and *TSC2* genes, form a complex that normally inhibits the mTOR pathway via inhibition of the intermediary GTP-binding protein Rheb. Upstream pathways activate or inhibit the mTOR pathway either directly or by interacting with the hamartin–tuberlin complex. For instance, in conditions of energy or nutrient surplus, growth factors, such as insulin, may trigger the PI3K/Akt pathway, which then stimulates the mTOR pathway and promotes increased cell growth and metabolism. By contrast, states of energy or nutrient deprivation may induce other upstream pathways, such as the LKB1/AMPK pathway, which ultimately inhibits mTOR activity and limits cell growth and metabolism. Alternative upstream and downstream regulators and complex feedback pathways also exist but are beyond the scope of this article [7–9].

While mTOR is essential for a number of important physiological functions, dysregulation of the mTOR pathway has been implicated in promoting a variety of disease states under pathological conditions. Perhaps the most clear example of a disease involving abnormal mTOR signaling is the genetic disorder, tuberous sclerosis complex (TSC). TSC is an autosomal dominant disease involving tumor or hamartoma formation in multiple organs, including cortical tubers and subependymal giant cell astrocytomas (SEGAs) in the brain [11,12]. While symptoms in TSC can vary depending on the organs involved, neurological manifestations usually account for the most disabling problems of TSC, including cognitive deficits, autism and intractable epilepsy. Mutations in two separate genes, *TSC1* and *TSC2*, have been found to cause TSC, encoding the proteins hamartin and tuberlin, respectively. As the hamartin–tuberlin complex normally inhibits the mTOR pathway, mutation of either *TSC1* or *TSC2* leads to abnormal disinhibition of the mTOR pathway. This hyperactivation of the mTOR pathway may result in increased cell growth and proliferation, which can promote tumorigenesis in TSC patients. Of direct translational relevance, clinical trials have shown that mTOR inhibitors can decrease growth of various tumors in TSC [13–16]. In fact, the mTOR inhibitor, everolimus, was recently approved by the US FDA as treatment for SEGAs in TSC patients. While the establishment of mTOR inhibitors as treatment for tumors in TSC is a significant advance, perhaps an even more important issue is whether mTOR inhibitors may also represent an effective therapy for the disabling neurological manifestations of TSC, including epilepsy. However, as the mechanisms of tumorigenesis and epileptogenesis may differ, the potential utility of mTOR inhibitors for epilepsy is not as well established.

In the remainder of this article, evidence for the role of mTOR inhibitors as either antiseizure (i.e., effective against seizures in patients that already have epilepsy) or anti-epileptogenic (i.e., effective in preventing epilepsy in high-risk patients that have not yet had a seizure or in reducing the severity and underlying progression of epilepsy in patients that

already have epilepsy) treatments will be reviewed (Tables 1 & 2). Much of the focus will logically be on epilepsy in TSC, but the potential for treatment of other, more common types of epilepsy will also be considered. As there are limited clinical studies in people, most of this analysis involves mechanistic data derived from animal models.

mTOR inhibitors as antiseizure drugs

Most current seizure medications primarily work by decreasing neuronal activity via direct modulation of ion channels or neurotransmitter receptors, such as sodium channels and GABA_A receptors. When effective, these drugs suppress seizures symptomatically, but have not been proven to have disease-modifying properties to prevent or reverse the development of epilepsy and the underlying mechanisms of epileptogenesis [2]. From a mechanistic standpoint, mTOR inhibitors do not appear to act like standard seizure medications. For example, rapamycin, when directly applied to neurons, has minimal or no acute effect on neuronal activity *in vitro* [17,18]. Nevertheless, while it is unlikely that mTOR inhibitors bind directly to ion channels, the mTOR pathway could be involved in regulating the expression of ion channels via effects on protein translation, which might secondarily decrease neuronal excitability. For example, mTOR inhibitors have been shown to increase the expression of potassium channels and decrease the expression of glutamate receptors [19,20].

A number of animal models of TSC have been developed, involving inactivation of the *Tsc1* or *Tsc2* gene in different cell populations in the brain, and many of these models have been documented to have seizures. In at least one model, mTOR inhibitors have been shown to have antiseizure effects in decreasing seizure frequency in mice that already have epilepsy [21]. Related to TSC, other animal models with robust epilepsy have been produced involving inactivation of the *Pten* gene, an upstream regulator of the mTOR pathway, which leads to abnormally increased mTOR activation. mTOR inhibitors have also been shown to decrease seizures in these *Pten* knockout mice [22–25]. Although the specific downstream mechanisms mediating these antiseizure effects are not established, it is clear that mTOR inhibitors can reduce or eliminate seizures in animals that have epilepsy caused by a genetic predisposition for elevated mTOR activity.

The potential antiseizure actions of mTOR inhibitors have started to be tested in patients with TSC. A couple of case reports have documented a decrease in seizure frequency in TSC patients with epilepsy after being started on an mTOR inhibitor for SEGAs [26,27]. Similarly, in a clinical study leading to the approval of everolimus for treatment of SEGAs, effects on seizure frequency were also examined as a secondary outcome measure and everolimus appeared to cause a significant decrease in seizure frequency in some TSC patients [14]. As these initial clinical studies could be confounded by an indirect effect of everolimus on seizures related to decreased SEGAs growth and hydrocephalus, another clinical trial was recently undertaken studying the effect of everolimus on seizures in TSC patients as the primary outcome measure, independent of SEGAs. Preliminary results from this uncontrolled trial also indicate that mTOR inhibitors can decrease seizure frequency in a subset of TSC patients; nine out of 17 (53%) patients had a greater than 50% reduction in seizures, including three patients that became seizure free [28]. While these preliminary data are encouraging, these findings still need to be confirmed in larger, placebo-controlled trials.

While it seems rational that mTOR inhibitors could be an effective treatment for TSC and other causes of epilepsy involving abnormal mTOR pathway activation, it is less clear whether mTOR inhibitors may be useful for other types of epilepsy. Again, based on known mechanisms of action, mTOR inhibitors may not have powerful antiseizure effects in pathological conditions that do not intrinsically feature abnormal mTOR signaling.

However, in a couple of animal models of epilepsy involving acquired brain injury, mTOR inhibitors do appear to decrease seizures. In the popular pilocarpine model, an episode of status epilepticus triggered by pilocarpine leads to brain injury and subsequent development of spontaneous seizures. In rats with spontaneous epilepsy following pilocarpine, rapamycin treatment significantly decreased seizure frequency [29]. Similarly, in a ‘multiple-hit’ rat model of symptomatic infantile spasms, rapamycin suppressed spasms and also improved cognitive outcome [30]. Furthermore, preliminary studies suggest that rapamycin has anticonvulsant effects on generalized seizures acutely induced by electrical stimulation or kainic acid [31]. Thus, it is possible that mTOR inhibitors may represent effective antiseizure treatment for a variety of types of epilepsy. However, a very recent study indicates that rapamycin may actually have pro-convulsant effects in immature rats in some seizure models, suggesting an age-dependent variability to rapamycin’s actions [32]. However, at this point, no clinical data have been reported on the antiseizure effects of mTOR inhibitors in other epilepsy patients besides TSC.

mTOR inhibitors as anti-epileptogenic drugs

While currently-available seizure medications have definite antiseizure effects, none have been proven to have disease-modifying or anti-epileptogenic properties in slowing or preventing the development of epilepsy, at least in people. For example, the popular seizure medications, phenytoin and valproate, may inhibit acute symptomatic seizures in the first couple of weeks following traumatic brain injury, but do not decrease the subsequent incidence of post-traumatic epilepsy [2]. Developing anti-epileptogenic drugs has been recognized as a top priority of epilepsy research for a number of years, but this point has not yet been realized in clinical practice [3]. There are a number of reasons to suspect that mTOR inhibitors could have anti-epileptogenic properties, at least for some types of epilepsy. While seizure generation most immediately involves mechanisms that directly control neuronal excitability, epileptogenesis is likely a much more complicated, diverse process involving more chronic mechanisms, such as synaptic and circuit reorganization, neuronal death, neurogenesis, gene and protein regulation and non-neuronal changes (e.g., inflammation, astrogliosis and the blood–brain barrier). Given the diverse roles of the mTOR pathway under physiological conditions (see above), it is reasonable to hypothesize that mTOR inhibitors could have anti-epileptogenic properties under pathological conditions, such as via inhibition of protein synthesis or anti-inflammatory actions.

In TSC, just as the mTOR pathway is important for tumorigenesis, mTOR could also promote epileptogenesis through parallel or distinct mechanisms [4–6]. A variety of pathological, cellular and molecular abnormalities have been identified in human brain specimens and animal models of TSC that at least correlate with epilepsy, such as the formation of giant cells, dysmorphic neurons, astrogliosis and altered glutamate transporter expression [11]. In the animal models, early treatment with rapamycin before the onset of seizures can prevent the development of epilepsy and many of the associated pathological and cellular abnormalities, consistent with a true anti-epileptogenic effect [21,33–36]. However, withdrawal of treatment results in the emergence of the seizures and other abnormalities, indicating that long-term treatment with mTOR inhibitors is necessary to maintain effectiveness. Based on this preclinical work documenting ‘proof-of-principle’, it would be reasonable to consider initiating a clinical trial testing whether mTOR inhibitors can prevent epilepsy in TSC patients. However, anti-epileptogenic drug trials are difficult to design and conduct for a number of reasons and thus no data on potential anti-epileptogenic effects of mTOR inhibitors currently exist in people (see the ‘Future perspective’ section).

Beyond TSC, there is also some basic science evidence that the mTOR pathway could be involved in mechanisms of epileptogenesis in other types of epilepsy and that mTOR

inhibitors could have broader potential as anti-epileptogenic treatment [4–6]. In models of acquired epilepsy due to brain injury following status epilepticus, rapamycin inhibits the development of mossy fiber sprouting and the associated hyperexcitability of hippocampal circuits, which is hypothesized to represent an epileptogenic mechanism causing temporal lobe epilepsy [29,37–40]. Rapamycin also has neuroprotective effects against neuronal death in a model of traumatic brain injury [41]. Some studies indicate that early treatment with rapamycin can inhibit the development of epilepsy in some of these models [39,40,42]. In addition, rapamycin may be effective in decreasing the development of aggressive behavior and autistic features associated with epilepsy [42,43]. However, there are some conflicting data and it appears that the anti-epileptogenic efficacy of mTOR inhibitors is highly dependent on a number of factors, such as the type of epilepsy model, dose and timing of treatment [44–46]. Furthermore, similar to TSC, when beneficial effects of mTOR inhibitors on pathological abnormalities or epilepsy have been documented, they appear to require continued treatment to maintain efficacy [29,47]. Thus, a number of issues need to be more clearly defined in preclinical models before considering anti-epileptogenic drug trials in patients at risk for acquired epilepsy. While there is evidence of abnormal mTOR activation in brain specimens of patients with non-TSC epilepsy, such as related to mesial temporal sclerosis [48], there have been no reports of the use of mTOR inhibitors in such patients.

Conclusion

The mTOR pathway may represent a rational new therapeutic target for epilepsy, based on its extensive role in regulating a variety of physiological and pathological mechanisms that may affect epileptogenesis and seizure generation. Preclinical data indicate that mTOR inhibitors have both antiseizure and anti-epileptogenic properties, especially in animal models of TSC, but potentially also in models of acquired epilepsy due to brain injury. Clinical studies from patients with epilepsy are much more limited, consisting simply of uncontrolled data supporting an antiseizure effect of mTOR inhibitors in TSC patients with established epilepsy. Larger, placebo-controlled trials are needed to determine more definitively whether mTOR inhibitors decrease seizure frequency in TSC patients. Furthermore, no published clinical data exist addressing whether mTOR inhibitors are effective in non-TSC epilepsy or have anti-epileptogenic properties in TSC patients. Therefore, many future basic and clinical studies are needed to define the role of mTOR inhibitors in the treatment of different types of epilepsy.

Future perspective

The basic science rationale and preclinical data for a possible role of the mTOR pathway in epilepsy, as well as initial clinical studies testing mTOR inhibitors, are strongest in TSC. Thus, in the next decade, there is the most hope for establishing mTOR inhibitors as a proven treatment for epilepsy in TSC patients. If the encouraging preliminary data from current uncontrolled clinical trials are confirmed [28], a placebo-controlled trial of an mTOR inhibitor for intractable epilepsy in TSC patients would be the reasonable next step. As mTOR inhibitors have already been approved for treating SEGAs in TSC patients and official indications for other TSC-related tumor types may soon follow, a positive result in a placebo-controlled epilepsy trial would greatly facilitate adding intractable seizures as another approved indication of mTOR inhibitors for TSC. Compared with most currently-available medications, the establishment of mTOR inhibitors as a treatment for seizures in TSC would be a unique mechanistic advance for the field of epilepsy, albeit a small subset of epilepsy patients.

Even if mTOR inhibitors are established as antiseizure treatments in TSC patients with intractable epilepsy, the available clinical data to this point suggests that their efficacy is

relatively modest, with most patients still experiencing seizures. Therefore, despite the unique mechanism of action, mTOR inhibitors may not turn out to be much more effective for intractable epilepsy in TSC than any of the other dozen new antiseizure drugs that have been approved over the past 20 years. By contrast, mTOR inhibitors have the potential to have a much greater clinical impact if they can be demonstrated to have anti-epileptogenic properties in TSC patients. No disease-modifying therapies have yet been established for epilepsy and anti-epileptogenic drug trials face a number of practical barriers, including difficulty in identifying an appropriate target population. TSC patients may, in fact, represent an ideal group to develop and test an anti-epileptogenic therapy for preventing epilepsy. While many epilepsy patients present unpredictably with their first seizures without any prior known risk factors, a subset of TSC patients are identified at a young age before the onset of epilepsy due to non-neurological findings of TSC [49]. Thus, it is feasible to identify and start a preventative treatment on this group of TSC patients. Furthermore, some identifiable risk factors may only engender a moderate risk of future epilepsy, such as approximately 20% prevalence of post-traumatic epilepsy following significant head trauma. By contrast, TSC patients are at high risk (~80–90%) of developing epilepsy [50], thus making it easier to justify exposing asymptomatic patients to a preventative treatment with potential side effects.

A number of other issues still need to be addressed before considering an anti-epileptogenic drug trial of mTOR inhibitors in TSC patients. First, even if mTOR inhibitors have anti-epileptogenic properties, the duration of treatment required to maintain effectiveness is not clear, especially in TSC. For TSC-related tumors, cessation of treatment seems to result in a regrowth of tumors [13,15]. As TSC is a genetic disease and mTOR inhibitors do not correct the underlying genetic defect driving mTOR hyperactivation, chronic, potentially life long, treatment may be necessary for TSC patients. On the other hand, for certain manifestations of TSC, such as epilepsy, a critical window may exist during which more limited treatment with mTOR inhibitors may be sufficient for prevention. Additional studies in animal models may help to define the minimal duration of treatment that maintains efficacy. Of course, the main concern and downside regarding any treatment are adverse effects. Significant side effects may occur with mTOR inhibitors, including chronic immunosuppression and associated opportunistic infections. Furthermore, at least in theory, mTOR inhibitors may interfere with critical developmental and learning mechanisms in the brain, such as synaptic plasticity and long-term potentiation [51]. One potential option to alleviate this concern would be to use ‘drug holidays’ or treatment paradigms with intermittent application of mTOR inhibitors. Animal model data suggest that the intermittent use of mTOR inhibitors can maintain efficacy, but reduce the risk of side effects, such as immunosuppression [24,52–54]. Finally, while a large proportion of TSC patients will develop epilepsy, a subset will not, thus exposing such patients to unnecessary treatment. Ideally, biomarkers could first identify those patients that are at highest risk for epilepsy and the best candidates for an anti-epileptogenic therapy. Although such biomarkers for epilepsy have not been definitively identified, future studies may establish specific EEG, brain MRI or biochemical abnormalities as biomarkers for epilepsy in TSC.

Beyond TSC, other high-risk populations, such as patients with traumatic brain injury, might, in principle, be candidates for anti-epileptogenic treatment with mTOR inhibitors. However, expansion to these non-TSC epilepsies should await more definitive data from animal models that better define the specific conditions and types of epilepsy that would benefit from mTOR inhibitors. As mTOR has also been implicated in a variety of other neurological and systemic disorders besides epilepsy [55–57], there is reason to hope that ongoing progress in basic and clinical research may support the utility of mTOR inhibitors for neurological diseases besides TSC.

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Executive summary

Background

- Current medications for epilepsy have significant limitations, including medical intractability and lack of disease-modifying properties.
- As current medications primarily regulate ion channels and neurotransmitter receptors, future, more effective treatments for epilepsy need to target completely different mechanisms of epileptogenesis.

Mammalian target of rapamycin pathway

- The mammalian target of rapamycin (mTOR) pathway is involved in a variety of important physiological and pathological processes in the brain.
- mTOR may represent a rational target as either an antiseizure or anti-epileptogenic treatment for epilepsy.

Antiseizure effects

- Preclinical data in animal models and initial, uncontrolled clinical studies suggest that mTOR inhibitors might be an effective antiseizure therapy for patients with intractable epilepsy caused by the genetic disease, tuberous sclerosis complex (TSC).
- Animal model data also suggest that mTOR inhibitors could have antiseizure effects against other types of seizures/epilepsy besides TSC.

Anti-epileptogenic effects

- In animal models of TSC, mTOR inhibitors have anti-epileptogenic properties in preventing epilepsy, although long-term treatment is necessary to maintain efficacy.
- Some preclinical studies suggest that mTOR inhibitors may have anti-epileptogenic properties in acquired epilepsy secondary to brain injury, but other studies have been negative, indicating that these effects are limited to specific conditions or types of epilepsy.
- Future basic science and clinical studies will help define the potential range of indications of mTOR inhibitors for epilepsy, most likely involving TSC, but possibly also other types of epilepsy.

Figure 1. Regulation of the mammalian target of rapamycin pathway

The mTOR is a serine–threonine protein kinase, which forms two complexes, rapamycin-sensitive mTORC1 and relatively rapamycin-insensitive mTORC2 (not shown). mTORC1 stimulates downstream signaling mechanisms involved in ribosomal biogenesis (S6K and ribosomal S6) and protein translation (4E-BP1 and eIF4E). Primarily through regulation of protein synthesis, the mTOR pathway modulates a variety of important physiological functions, such as cell growth and proliferation, metabolism and brain-specific processes. By similar mechanisms, the mTOR pathway may influence epileptogenesis under pathological conditions (e.g., synaptic reorganization, ion channel expression and neuronal death). In turn, the mTOR pathway may be activated or inhibited by various physiological or pathological stimuli via various upstream signaling pathways and intermediary proteins (TSC1, TSC2 and Rheb). Genetic mutations in different elements of these upstream pathways (*TSC1*, *TSC2*, *PTEN* and *STRADα*) have been identified that cause

hyperactivation of the mTOR pathway and may lead to various disease phenotypes, including epilepsy. Adapted with permission from [58].

Table 1

Potential antiseizure effects of mTOR inhibitors in clinical studies and animal models.

Epilepsy type/model	Effect on seizures	Proposed mechanism(s) of action	Ref.
<i>Clinical studies</i>			
Tuberous sclerosis complex with intractable epilepsy	Reduction in seizure frequency in tuberous sclerosis complex patients	Unknown	[14,26–28]
<i>Animal models</i>			
Tuberous sclerosis complex knockout mice	Reduction in chronic seizure frequency in <i>Tsc1</i> knockout mice after the onset of epilepsy	Inhibition of cell growth/proliferation and restored astrocyte glutamate transport	[21]
<i>Pten</i> knockout mice	Reduction in chronic seizure frequency and duration in <i>Pten</i> knockout mice after the onset of epilepsy	Decreased megalencephaly and cell size	[22–25]
Pilocarpine status epilepticus	Reduction in chronic spontaneous seizure frequency in rats following status epilepticus	Inhibition of mossy fiber sprouting	[29]
Multiple-hit model of infantile spasms	Reduction in acutely induced spasms in rats	Unknown	[30]
Maximal electroshock threshold	Reduction in severity and duration of acutely induced seizures in mice	Unknown	[31]
Kainate-induced acute seizures	Reduction in severity and duration of acutely induced seizures in mice	Unknown	[31]

Table 2

Potential antiepileptogenic effects of mTOR inhibitors in animal models.

Epilepsy type/model	Effect on epilepsy	Proposed mechanism(s) of action	Ref.
Tuberous sclerosis complex	Prevention of epilepsy in <i>Tsc</i> knockout mice when initiated prior to onset of seizures	Inhibition of cell growth/proliferation, restoration of astrocyte glutamate transport, reduction in inflammation/endoplasmic reticulum stress and restoration of myelination	[21,33–36]
Kainate status epilepticus model of temporal lobe epilepsy	Reduction in frequency of spontaneous seizures in rats following status epilepticus	Inhibition of mossy fiber sprouting	[39]
Pilocarpine status epilepticus model of temporal lobe epilepsy	Reduction in mossy fiber sprouting, but no effect on spontaneous seizures in mice	Inhibition of mossy fiber sprouting	[37,44]
Angular bundle electrical stimulation model of temporal lobe epilepsy	Reduction in frequency of spontaneous seizures in rats following status epilepticus	Inhibition of mossy fiber sprouting, reduction in neuronal death and decrease in blood–brain barrier leakage	[40]
Amygdala electrical stimulation model of temporal lobe epilepsy	No effect on spontaneous seizures in rats following status epilepticus	No effect on mossy fiber sprouting	[45]
Neonatal hypoxia	Reduction in chronic seizures in rats following hypoxic neonatal seizures	Inhibition of enhanced glutamate excitatory postsynaptic currents	[42]