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Review

Mechanistic target of rapamycin (mTOR) signaling in status epilepticus

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ABSTRACT

The mechanistic target of rapamycin (mTOR) pathway plays a critical role in brain development, neuronal shape and size, and synaptic plasticity, as well as learning and memory. Mutations in mTOR pathway genes (MPG) cause malformations of cortical development (MCDs) that are highly associated with often intractable epilepsy, thus highlighting an association between the mTOR pathway and establishment of the epileptic network. A growing body of preclinical evidence in in vitro and rodent model systems suggests that mTOR signaling may be altered in status epilepticus (SE) and that modulation of mTOR activation with mTOR inhibitors such as rapamycin (sirolimus) could provide new therapeutic avenues for treatment of both refractory epilepsy and SE. Rapamycin may have ubiquitous effects on all neuronal subtypes as well as astrocytes and seems to prevent the development of seizures following experimentally induced SE. To date, there have been no human studies focused on mTOR signaling in SE, but clearly, preclinical data support investigation into this pivotal cell signaling pathway. Thus, modulation of the mTOR pathway may provide a new strategy for treatment of SE and could have implications for the prevention of epilepsy in patients with SE.

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1. Introduction

The mechanistic target of rapamycin (mTOR) pathway has emerged as a pivotal cell signaling cascade in a variety of human epilepsy syndromes, especially in association with malformations of cortical development (MCDs) such as tuberous sclerosis complex (TSC), focal cortical dysplasia (FCD), hemimegalencephaly (HME), and megalencephaly (ME) [1,2]. Malformations of cortical development caused by mutations in MPG have been grouped as "mTORopathies" [1,2]. The paradigm mTORopathy is TSC in which inherited or sporadic loss-of-function mutations in *TSC1* or *TSC2* result in constitutive mTOR hyperactivation in the fetal brain and the formation of FCDs (cortical tubers) that are highly associated with infantile spasms, epilepsy, autism, and intellectual disability [3]. Interestingly, mutations affecting all vectors of the mTOR cascade, i.e., canonical growth factor signaling, adenosine monophosphate/adenosine triphosphate (ATP/AMP), and amino acid signaling that culminate in enhanced mTOR signaling lead to brain hyperexcitability and seizures.

It has become clear that the mTOR pathway is critical to the regulation of neuronal excitability, as seizures are the *sine qua non* feature of mTORopathies. A role for mTOR signaling in status epilepticus (SE) is less well-defined, although a number of preclinical studies in rodent models have clearly implicated mTOR in both SE and the establishment of an epileptic network. In addition, it is highly likely that the mTOR pathway is at least implicated in SE since many patients with TSC or other mTORopathies are at risk for SE. In view of the recent clinical success of mTOR inhibitors such as everolimus in seizure reduction in TSC [4], it seems plausible that these drugs could become part of our clinical armamentarium for the treatment of SE in patients with a broad range of mTORopathies. What is less clear is whether this class of drugs will be useful in all types of SE and indeed, should the mTOR pathway be investigated and targeted more broadly in SE?

2. The mTOR pathway

Mechanistic target of rapamycin (280 kD) is a serine/threonine kinase encoded by the *MTOR* gene (chromosome 1p36). The catalytic kinase domain of mTOR is within the carboxy-terminal region of mTOR. In contrast, there are tandem HEAT (Huntingtin, elongation factor 3 (EF3), protein phosphatase 2A (PP2A), and TOR1) repeats and a FAT (Focal Adhesion Kinase, Targeting) domain for protein–protein interactions within the N-terminal region that allows binding of regulatory-associated protein of mTOR (Raptor) and rapamycin-insensitive

Abbreviations: FCD, focal cortical dysplasia; HME, hemimegalencephaly; KA, kainic acid; MCD, malformation of cortical development; mTOR, mechanistic target of rapamycin; MPG, mTOR pathway genes; ME, megalencephaly; SE, status epilepticus; TSC, tuberous sclerosis complex.

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companion of mTOR (Rictor) that distinguish the mTORC1 from mTORC2 complexes, respectively [5]. The macrolide antibiotic rapamycin (sirolimus) and its synthetic analog everolimus are potent inhibitors of mTORC1 that bind to FK506-binding protein (FKBP12) that in turn binds allosterically to mTOR and inhibits its serine/threonine kinase activity. The mTOR signaling plays a pivotal role in T-cell activation within the immune system, and rapamycin has been shown to diminish T-cell migration and activation. Thus, mTOR inhibitors are immunomodulatory agents, and indeed, initial uses for sirolimus were to prevent rejection of transplanted organs. mTORC1 (versus mTORC2) has the most documented relevance to epilepsy, and it functions in the modulation of protein translation, ribosomal biogenesis, and nutrient transport. In the brain, mTORC1 has distinct functions referable to neuronal excitability, memory formation, and learning. mTORC1 has a dynamic subcellular localization moving between the cytoplasm, lysosome, endoplasmic reticulum, and nucleus; the active signaling conformation occurs when mTORC1 is tethered to the lysosomal membrane [6].

Mechanistic target of rapamycin modulates messenger RNA translation and cell growth through phosphorylation of p70S6K and 4E (eIF4E)-binding protein 1 (4E-BP1). Phosphoactivation of p70S6 kinase leads to phosphorylation of ribosomal S6 protein, a key ribosomal protein that functions in protein translation. 4E (eIF4E)-binding protein 1 directly interacts with eukaryotic translation initiation factor 4E, part of the large complex that targets 40S ribosomal subunits to the 5′-end of mRNAs. When 4E-BP1 interacts with eIF4E, translation is inhibited. Phosphorylation of p70S6 kinase, ribosomal S6, and 4E-BP1 proteins serves as common "readouts" of increased mTOR signaling in both in vitro and in vivo systems. Mechanistic target of rapamycin has also been implicated in purine and pyrimidine nucleotide biosynthesis, DNA transcription, and phosphorylation of other protein substrates [7].

In the brain, the mTOR pathway plays pivotal roles in the establishment of neuron shape and size, dendritic arborization, axon outgrowth, and synaptic structure [8]. For example, the mTOR signaling pathway promotes the growth and branching of dendritic arbors in hippocampal neurons in vitro. The mTOR pathway regulates excitatory and inhibitory neurotransmission. For example, in *Pten* knockout (KO) mice, mTOR signaling increases evoked synaptic responses, the number of synaptic vesicles, and the number of synapses formed in both glutamatergic and GABAergic neurons [9]. Rapamycin prevented these changes and also decreased synaptic transmission in wild-type glutamatergic, but not GABAergic, neurons, suggesting that there may be some cellular specificity for mTOR inhibition effects. The mTOR signaling modulates learning and memory processes via regulation of long-term potentiation (LTP) and long-term depression (LTD). Disruption of mTOR signaling by rapamycin results in a reduction of late-phase LTP expression induced by high-frequency stimulation; the early phase of LTP is unaffected [10,11]. This divergent effect likely reflects effects of mTOR inhibition on protein synthesis, a key mechanism responsible for late- but not early-phase LTP. Rapamycin also blocks the synaptic potentiation induced by brain-derived neurotrophic factor in hippocampal slices. Activation of mTOR signaling cascade is required for metabotropic glutamate receptor-long term depression (mGluR-LTD) and suggests that this pathway may couple group I mGluRs to translation initiation in hippocampal area CA1 [11]. Mechanistic target of rapamycin has been implicated in synaptic plasticity and local protein translation in dendrites triggered by synaptic activity [11]. For example, rapamycin increased translation of endogenous Kv1.1 mRNA in dendrites and expression of the Kv1.1 voltage-gated potassium channel in hippocampal neuronal dendrites but not axon [12,13]. This finding may suggest a mechanism for antiseizure effects of mTOR inhibitors since the loss of Kv1.1 in animal models has been linked to seizures. In summary, mTOR plays pivotal roles in excitation and inhibition, plasticity, and local protein synthesis in neurons.

3. mTORopathies

Mutations in a number of mTOR pathway genes (MPG) including *AKT3*, *DEPDC5*, *KPTN MTOR*, *NPRL3*, *NPRL2*, *PI3K*, *PTEN*, *TSC1*, *TSC2*, *TBC1D7*, *RHEB*, *STRADA*, and *SZT2* have been associated with MCD [14]. These encoded proteins signal through mTOR and either inactivating or activating mutations are all associated with enhanced mTOR signaling. Of course, a major unanswered question is whether all of the effects of these mutations on brain development and network integrity are indeed funneled through mTOR, i.e., are fully mTOR dependent. The majority of HME and FCD cases reported are linked to de novo, somatic mutations occurring during brain development rather than germline mutations. The enrichment of allelic variants in MCD tissue specimens analyzed after resection for epilepsy treatment ranges from very low (~1%) to more pronounced (~30%) suggesting that in most MCD resulting from somatic mutations, a significant proportion of neurons do not contain mutations and are thus genetically intact. This has important mechanistic implications since FCD and HME reflect tissue mosaics of cells containing somatic mutations as well as cells (bystanders) that have a normal genotype.

The central tenet for conceptualizing mTORopathies is that mutations in distinct MPG within the mTOR pathway culminate in phenotypic features including abnormal neuronal morphology, disorganized cortical lamination, clinically, seizures. In many, though certainly not all cases with MPG mutations, histological evidence of mTOR signaling activation evidenced by hyperphosphorylation of the ribosomal S6 protein (P-RS6) downstream of mTOR is observed, and thus, an important unanswered question is whether all identified MPG mutations actually activate mTOR to the same extent. A critical limitation to our understanding of mTORopathies is that few MPG variants have been directly validated. Thus, in some mouse models using either knockdown, knockout, or overexpression of MPG, increased mTOR signaling may lead to neuronal hyperexcitability and in a small number of models, clinical seizures, i.e., *PTEN* mutants. However, seizures are not seen in all models. Indeed, while most individuals with MCD resulting from a MPG mutation exhibit seizures clinically, there is large variation in epilepsy phenotypes, spanning infantile spasms to medically controlled seizures. Thus, an important unanswered question is how MPG variants yield an epilepsy phenotype and whether all seizure phenotypes are mTOR dependent. While in some models, there is reversibility of both structural, e.g., altered cortical lamination, and functional effects, e.g., hyperexcitability and seizures, of these mutations by pharmacological mTOR inhibition with rapamycin or related compounds [15–17], in others, the effects are less pronounced. However, the mechanisms through which MPG mutations lead to changes in brain structure and hyperexcitability remain to be fully explained since the role of most MPG variants in mTOR activation has not been rigorously investigated.

4. mTOR in SE

Much of what we know about the role of mTOR signaling in SE is inferential from studies using defined SE models to study epileptogenesis and the establishment of the epileptic network. These models include lithium–pilocarpine, kainic acid (KA), pentylenetetrazol, and direct electrical stimulation. To date, there have been no studies in humans on mTOR signaling in SE, i.e., no histopathological analyses of human tissue, no clinical trials of mTOR inhibitors in SE in humans (searching ClinicalTrials.gov), no case reports using mTOR inhibitors in humans, and very few series evaluating the incidence, outcomes, and mechanisms of SE in mTORopathies such as TSC. Clearly, the role of mTOR in human SE remains to be more fully defined.

Several animal model studies have addressed how the mTOR pathway might contribute to SE. Early studies demonstrated that mTOR signaling was enhanced in mice as early as 2 h following KA-induced SE as evidenced by enhanced phosphorylation of ribosomal S6 and Akt [18]. Using a KA-induced SE model in rats,

a biphasic response of the mTOR pathway was observed with a first activation seen within 1–6 h post-SE and then a second peak in activity from 3 days to several weeks following SE [19]. The second peak of mTOR activation resolved by 5 weeks post-SE. Interestingly, in this paradigm, rapamycin had no effect on acute seizures caused by KA but diminished subsequent spontaneous seizures following SE, suggesting an effect of mTOR signaling on epileptogenesis. These investigators postulated a model in which a variety of brain insults, i.e., traumatic brain injury, led to hyperactivation of mTOR signaling akin to loss of TSC1 or TSC2 in TSC. In another study, pilocarpine-induced SE led to rapid activation of mTOR signaling within 30 min, an effect that was blocked by rapamycin administration [20]. In fact, these authors showed that rapamycin could not stop recurrent spontaneous seizures caused by pilocarpine. Administration of KA to rats caused a rapid but regionally selective increase in mTOR activation within the hippocampal CA1 subfields and dentate gyrus and piriform cortex [21]. In an interesting TSC model, *Tsc1* was conditionally inactivated in rat brain using a tamoxifen-inducible cyclic recombinase (CRE) system [22]. In these animals, seizures began within 2 days of Tsc1 inactivation and progressed to SE and death within a week. Pretreatment with rapamycin abrogated this SE phenotype in these animals.

A number of studies have demonstrated a robust inflammatory response in brain tissue during and following SE [23]. Thus, since one well-known biological effect of mTOR inhibition is decreased, T-cell migration and cellular inflammatory responses (mTOR inhibitors are potent inhibitors of postorgan transplantation rejection), analysis of the roles of rapamycin in inflammation in SE has been reported. For example, two studies focused on the role of rapamycin on immune activation in rodent SE models. Inhibition of mTOR reduced epileptogenesis and blood–brain barrier leakage but not microglia activation following angular bundle stimulation-induced SE in rats [24]. Rapamycin reduced the development of seizures, SE-induced neuronal cell loss, mossy fiber sprouting, and blood–brain barrier leakage but had no effect on hippocampal microglia/astrocyte activation. Following pilocarpine-induced SE, rapamycin suppressed mTOR activation, microglial activation, and reactive astrocytosis [25]. Thus, one possible mechanism for antiseizure effects of mTOR inhibitors is via immunomodulation and antiinflammatory pathways.

There has been some contrasting evidence for the effects of rapamycin on seizures following SE. For example, rapamycin treatment within 24 h of pilocarpine SE in mice suppressed mossy fiber sprouting, but there was no change in spontaneous seizure frequency [26]. In addition, there was no effect of rapamycin on granule cell proliferation, hilar neuron loss, or generation of ectopic granule cells. These studies suggest that mTOR pathway inhibition may alter SE and recurrent seizures following SE. Interestingly, rapamycin has few immediate effects on cell firing in vitro. For example, treatment of rat hippocampal neuron in vitro with rapamycin induces no changes in baseline firing or resting membrane potential [27]. In rodent brain, rapamycin altered the firing rates of layer 5 pyramidal neurons in acute brain slices [28]. Using the National Institute of Neurological Disorders and Stroke (NINDS) Anticonvulsant Screening Project Protocol [29], rapamycin protected against maximal electric shock threshold (MES-T) seizures (THLE) at 3 and 6 h of treatment, but rapamycin did not protect against 6-Hz seizure test at 3 and 6 h of treatment. Rapamycin hastened the onset of seizures following KA acutely but protected against spontaneous seizures with prolonged treatment. Interestingly, rapamycin did not protect against pentylenetetrazol (PTZ-induced) seizures. These authors concluded that the efficacy of rapamycin as an acute anticonvulsant agent may be limited but that mTOR pathway modulation may alter the development of seizures following SE.

In summary, pilocarpine, electrical stimulation, and KA SE induce mTOR activation in the hippocampus and cerebral cortex (Fig. 1). Rapamycin blocks mTOR activation post-SE, rescues some pathological features post-SE, prevents altered blood-brain barrier (BBB) permeability post-SE, decreases microglial activation post-SE, has variable effects on seizures induced by SE, has cell specific effects on cell firing/excitability. In contrast, rapamycin does not block acute seizures caused by pilocarpine, KA, 6-Hz stimulation, or PTZ.

5. Treatment approaches with mTOR inhibitors

In view of the preclinical data supporting a possible role for the mTOR cascade in SE, a logical question is how mTOR inhibitors might be implemented for the treatment of SE? Currently, everolimus is FDA-approved for the treatment of seizures in TSC as adjunctive therapy to conventional anti-epileptic drugs (AEDs) based on compelling data from the EXIST-3 trial [4,29]. Other series have demonstrated efficacy of mTOR inhibitors such as sirolimus for intractable epilepsy associated with *TSC1/2* [30] and *STRADA* [31] gene mutations. An obvious consequence of the implementation of mTOR inhibitors for mTORopathies such as TSC might be that there will be less SE in these disorders. Other potential indications for mTOR inhibitors might include SE due to traumatic brain injury, stroke, brain cancer, and intracerebral hemorrhage based on findings in preclinical models of these disorders of

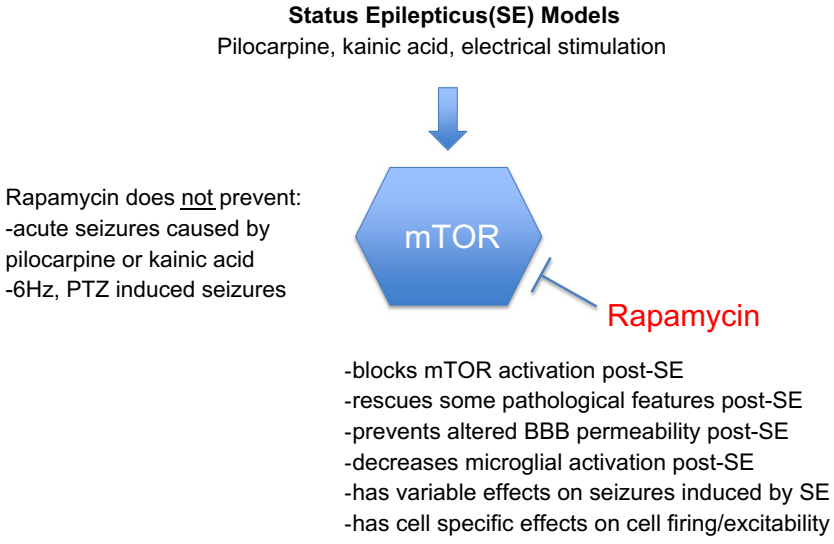

Fig. 1. Schematic depicting a role for mTOR in status epilepticus models. PTZ, pentylenetetrazol.

elevated mTOR signaling. An exciting possibility, yet untested, might be the use of mTOR inhibitors for autoimmune and paraneoplastic encephalitis since this class of drugs has effects on network excitability and have potent immunosuppressant effects. Thus, sirolimus or everolimus might serve to control seizures and SE in autoimmune and paraneoplastic encephalitis as well as serving as disease-modifying therapies to mitigate the inflammatory response in the brain. Finally, mTOR inhibitors could be considered for SE syndromes with presumed autoimmune mechanisms such as febrile infection-related epilepsy syndrome (FIRES) and new onset refractory status epilepticus (NORSE).

A pivotal unanswered question is how mTOR inhibitors would be dosed in these novel and untested clinical scenarios? To date, there are several dosing strategies for mTOR inhibitors currently available based on the indication including breast and renal cancer, postorgan transplant and acute rejection, hamartoma and lymphangioleiomyomatosis in TSC, and epilepsy in TSC. Currently, sirolimus is available as a pill formulation or in oral solution (there is no i.v. preparation) and, thus, could be dosed in awake or unconscious individuals. The time to serum steady state is approximately 5–7 days with a serum half-life of ~60 h. Mechanistic target of rapamycin inhibitors as a class of drugs have few drug–drug interactions, although their metabolism is enhanced when coadministered with CYP3A inducers. The side effect profile of mTOR inhibitors ranges from Grade I serious adverse events (aphthous oral ulcers, nausea, diarrhea) to Grade IV events with hyperlipidemia, dysmenorrhea, interstitial pneumonitis, and immunodeficiency [32]. Some of these effects are dose-dependent, while others are idiosyncratic.

6. Conclusions

There is substantial preclinical data that mTOR inhibitors could play a critical role in the treatment of SE and subsequent establishment of the epileptic network. The next logical step in deploying what could prove to be a new therapeutic approach to SE in a variety of neurological disorders would be to design and implement first-in-class clinical trials. The side effects of profiles of these agents have been well-defined in previous trials so rapid Phase I trials, to determine if these agents cause particular serious adverse events (SAEs) in each novel indication, could pave the way for Phase II and III trials in larger cohorts designed to assess efficacy both for SE and subsequent development of seizures.

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Declaration of competing interest

The author has no conflict of interest.

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