MINI REVIEW

RECORDS OF PHARMACEUTICAL AND BIOMEDICAL SCIENCES

Role of m-TOR pathway in epilepsy: A review and consideration

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Abstract

Current antiepileptic drugs (AEDs) have many limitations. They act only as a symptomatic treatment (anticonvulsant) and lacking antieplitogenic properties, they have a lot of adverse effects and drug drug interactions, In addition, nearly a third of patients with epilepsy have seizures refractory to current medical therapies. In search for novel targets, m-TOR signaling was found to be involved in major multiple cellular functions, including cell survival, growth, protein synthesis, synaptic plasticity and other cellular processes related to epileptogenesis. This made mTOR a possible therapeutic target for epilepsy treatment. This review explores the relevance of m-TOR pathway to epileptogenesis and presents the effects of m-TOR inhibitors in some animal models of epilepsy.

Keywords: Epilepsy, m-TOR inhibitors, epileptogeneisis, AEDs

1. Introduction

Epilepsy is one of the most common neurological disorders that affecst more than 60 million people worldwide. It is characterized by excessive neuronal firing resulting in uncontrolled convulsions (Wei et al., 2015). Although epilepsy can be well controlled in most patients through administration of antiepileptic drugs (AEDs), nearly 30% of patients develop resistance to the available medications (Kwan and Brodie 2000). The mechanisms of action of current antiseizure medications focus mainly on regulating neurotransmitters and ion channels. The development of effective treatments for drug-resistant epilepsy depends mostly on targeting novel mechanisms of action that are largely different than current ones (Ostendorf and Wong 2015). The molecular background of epileptogenesis is complex, and in many cases condition specific, but some mechanisms appear to be common in many types of epilepsy. Abnormal activity of mTOR (mammalian target of rapamycin) pathway was found to play an important role in epileptogenesis (Sadowski et al., 2015).

Many experimental models of genetic and acquired epilepsy, in which mTOR hyperactivation was evidenced, are responsive to mTOR inhibitors (Huang et al. 2010; Leo et al. 2016). This supports the theory that dysregulation of the mTOR pathway is crucial for the development of epileptogenesis and epilepsy.

2. Molecular signaling pathways in epileptogenesis

The possibility that brain injury or genetic abnormality might lead to the development of epilepsy throughout molecular signaling pathways is compelling, as it would suggest that intervention of these pathways may be capable of modifying the epileptogenic process before the appearance of seizures. Research is attempted to determine molecular signaling processes that might be involved in the formation of the aberrant neuronal discharge found in the epileptic brain, including features such as axonal sprouting and cell death that develop following a delay after an initial brain insult. Brain-derived neurotrophic factor (BDNF)-

ropomyosin-related kinase B (TRKB; also known as NTRK2) signaling, the mTOR pathway, the REST pathway and other transcriptional regulators were found be important (Goldberg and Coulter 2013).

3. Mammalian target of rapamycin (m-TOR) and epilepsy

mTOR is a serine/threonine protein kinase that forms part of two intracellular signaling complexes, mTORC1 and mTORC2 (Griffith and Wong 2018). It is involved in multiple basic cellular functions, including cell growth, proliferation and survival in response to both extracellular and intracellular upstream signals such as growth factors, insulin and cellular stressors such as hypoxia, osmotic stress, reactive oxygen species, viral infection or the availability of nutrients and energy (Corradetti and Guan 2006; Bhalla et al. 2017) as illustrated in figure 1.

m-TOR is a component of the phosphatidylinositol 3-kinase (PI3K) pathway (Zarogoulidis et al. 2014). mTOR regulates protein synthesis through phosphorylation and inactivation of the repressor of mRNA translation, eukaryotic initiation factor 4E-binding protein (4E-BP1), and through the phosphorylation and activation of S6 kinase (S6K1) allowing eIF3 to bind eIF4G (Takei and Nawa 2014; Hay and Sonenberg 2004). 4E-BP1 (and probably 4E-BP2) are strong candidates for linking mTORC1 signaling to cell transformation (Fonseca and Proud 2010).

Some diseases as Tuberous sclerosis complex (TSC), are caused by genetic mutations in the molecules on the mTOR pathway produce syndromes that include epilepsy (Cho 2011). Adenosine monophosphate-activated protein kinase (AMPK) is a Ser/Thr kinase that is linked to mTOR signaling as well. It acts as master regulator that affects homeostatic processes such as autophagy and cell metabolism. mTORC1 is suppressed by AMPK both directly, through the phosphorylation of Raptor, and indirectly through the phosphorylation and activation of TSC2. mTORC1 signaling also found to regulate AMPK through negative feedback where S6K phosphorylate and inhibit AMPK (Garza-Lombó et al. 2018; Gwinn and Shaw 2010). Considering the critical role of mTOR in normal brain function, it is not surprising that dysregulation of the mTOR cascade has been found to be involved in many neurological disorders and could be responsible for the development of epilepsy (Leo et al. 2016; Griffith and Wong 2018). Ketogenic diet, a high fat and low carbohydrate diet, is a well-established treatment for intractable epilepsy since the 1920s (D'Andrea Meira et al. 2019). A study found that the hippocampus and liver of normal rats which were fed ketogenic diet showed a decrease in the expression of two markers that activate the mTOR pathway, phosphorylated ribosomal protein S6 (pS6) and phosphorylated acutely transforming retrovirus AKT8 in rodent T cell lymphoma (pAKT), suggesting possible association of the mTOR pathway effects with the effects of the ketogenic diet on seizures (Xf et al. 2013).

4. m-TOR dyregulation and epileptogenesis.

By studying the epileptogenic mechanism in different animal models, it was found that in tuberous sclerosis complex, mutation in either the TSC1 or TSC2 gene results in overactivation of mTOR leading to loss of function of the hamartin/tuberin complex.

Thus, this causes dysregulation of mTOR's downstream functions and this contribute to epileptogenesis. PTEN mutations result in loss of inhibition of PI3K/Akt signaling, which results in mTOR hyperactivation and seizures. Excessive glutamate release during status epilepticus or after trauma may result in NMDA receptor-mediated activation of PI3K/Akt signaling, which would be expectedto relieve the hamartin/tuberin inhibition of mTOR, causing a cascade of cellular events that likely contribute to epileptogensis (McDaniel and Wong 2011; Zeng et al. 2011; Nguyen et al. 2015) figure 2.

5. m-TOR inhibitors in animal models of epilepsy.

Current antiseizure medications appear to act only as symptomatic treatment in suppressing seizures, but none showed antiepileptogenic or disease-modifying effects for preventing the development of epilepsy in high risk patients or for slowing the underlying progression of epilepsy**.**

In the following table, evidence summarizes the role of mTOR signaling in the pathogenesis of epilepsy and that mTOR inhibitors have antiepileptogenic effects in different animal models of epilepsy (Wong, 2013).

Conclusion:

mTOR signaling pathway association with epilepsy and epileptogenesis will make it a therapeutic target for many researchers to study extensively in order to find a radical cure for epilepsy especially the refractory or resistant one.

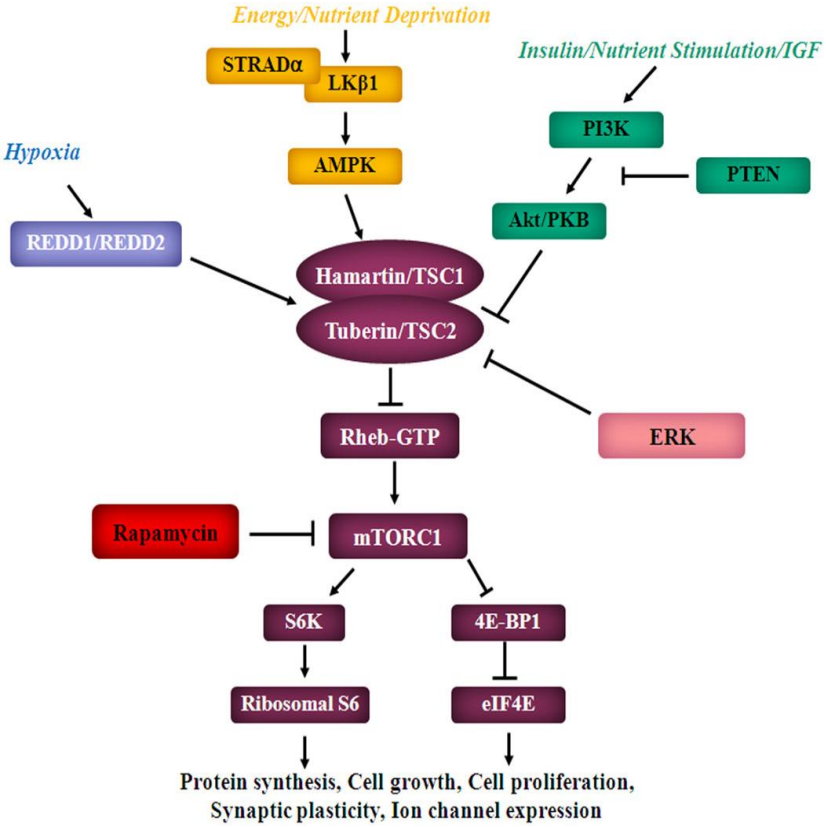

Figure 1: Regulation of mTOR signaling pathway (Ryther and Wong 2012)

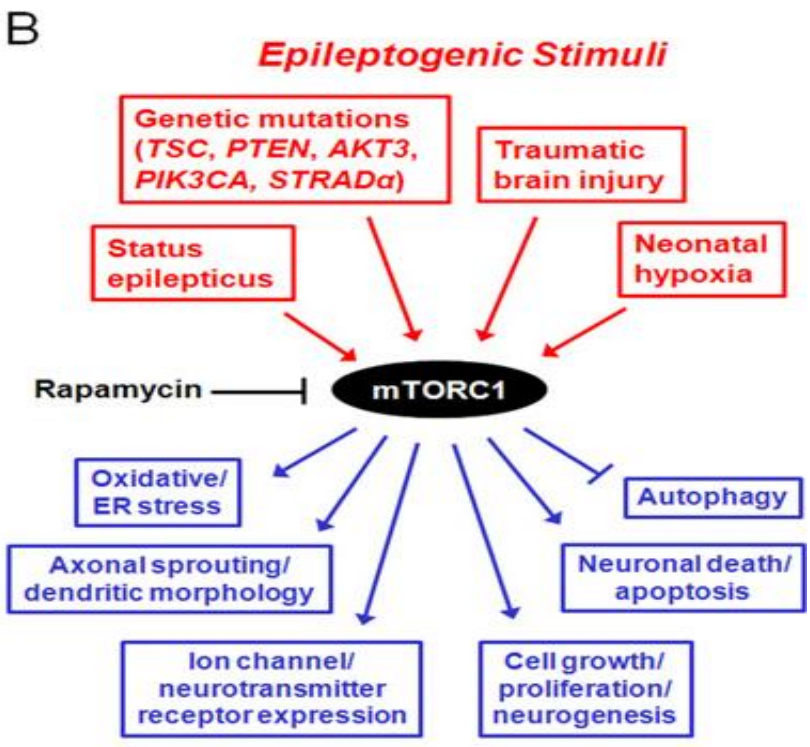

Figure 2: Mechanism of mTOR dysregulation and epilepsy.

Table 1: potential antiepileptogenic effects of mTOR inhibitors in animal models of epilepsy.

Epilepsy type/model	Effect on epilepsy	Suggested mechanism(s) of action	Reference
Tuberous sclerosis complex knock out mice	Prevention of epilepsy in *Tsc* KO mice when initiated prior to onset of seizures	Inhibition of cell growth/proliferation, restored astrocyte glutamate transport, decreased inflammation/ER stress, restored myelination	(Way et al. 2012)
kainate status epilepticus model of temporal lobe epilepsy	Reduction in frequency of spontaneous seizures in rats following status epilepticus	Inhibition of mossy fiber sprouting	(Zeng et al. 2009)
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	(Buckmaster and Lew 2011)
Angulat 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, decreased blood-brain barrier leakage	(Vliet et al. 2012)
Amygdala electrical stimulation model of temporal lobe epilepsy	No effect on spontaneous seizures in rats following status epilepticus.	no effect on mossy fiber sprouting	(Sliwa et al. 2012)
Neonatal hypoxia	Reduction in chronic seizures in rats following hypoxic neonatal seizures	Inhibition of enhanced glutamate EPSCs	(Talos et al. 2012)
WAG/Rij model of genetic absence epilepsy	Reduction in frequency of spike-wave discharges at 6 and 10 months of age after treatment with rapamycin from 45 d to	unknown	(Russo et al. 2013)

	5 mo in WAG/Rij rats.		
Controlled cortical impact injury model of posttraumatic epilepsy	Reduction in frequency of spontaneous seizures in mice following controlled cortical impact injury	Inhibition of mossy fiber sprouting, neuronal death	(Wong, 2013)

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